Effets de la chirurgie bariatrique sur les complications hépatiques de l'obésité

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EFFETS DE LA CHIRURGIE BARIATRIQUE SUR LES COMPLICATIONS HEPATIQUES DE L'OBESITE

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A mon jury de thèse

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Liste des Abréviations

AG : Acides Gras

AGB : Anneau Gastrique Ajustable

AGL : Acides Gras libres

AGPI : Acides Gras polyinsaturés

AgRP : Agouti Related Peptide

ALA : Acide α-Linolénique

ALAT : Alanine Amino Transférase

ATP : Adénosine TriPhosphate

CART : Cocaine & Amphetamine-Related Transcript

CCK : CholéCystoKinine

CHC : Carcinome HépatoCellulaire

ChREBP : Carbohydrate Responsive Element-Binding Protein

CHS : Cellules Hépatiques Stellaires

DAMP : Damage-Associated Molecular Patterns

DHA : Acide DocosaHexaénoïque

DT2 : Diabète de Type 2

EPA : Acide EicosaPentaénoïque

GLP-1 ou 2 : Glucagon Like Peptide 1 ou 2

HDL : High Density Lipoprotein Cholestérol

HTA : Hypertension Artérielle

HFD : High Fat Diet

IL : Interleukine

IMC : Indice de Masse Corporelle

IRS : Récepteur à l'insuline

LPS : LipoPolySaccharide

α-MSH : α-Melanocyte-Stimulating Hormone

MCP-1 : Monocyte Chemotactic Protein 1

NA : Noyau Arqué

NAFLD : Non-Alcoholic Fatty Liver Disease

NASH : Non-Alcoholic SteatoHepatitis

NF-κB : Nuclear Factor-kappa B

NKT : Cellules T « Natural killer »

NPY : NeuroPeptide Y

PAMP : Pathogen-Associated Molecular Patterns

PI3K : PhosphoInositide 3-Kinase

POMC : Pro-Opio-MélanoCortine

PPAR : Peroxisome Proliferator-Activated Receptor

PPE : Pourcentage de Perte de Poids en Excès

PYY : Peptide tyrosine tyrosine 3-36

PRR : Pattern-Recognition Receptors

RE : Réticulum Endoplasmique

ROS : Reactive Oxygen Species ou espèces réactives de l'oxygène

RYGBP : Gastric ByPass en Roux-en-Y

SAS : Syndrome des Apnées du Sommeil

Score NAS : Non-Alcoholic Fatty Liver Disease Activity Score

SD : Dérivation Bilio-Pancréatique avec Switch Duodénal

SG : Sleeve Gastrectomie

SM : Syndrome Métabolique

SNC : Système Nerveux Central

SREBP-1c : Sterol Regulatory Element-Binding Protein)

TA : Tissu Adipeux

TG : Triglycérides

TLR : Récepteurs Toll-like

TNF-α : Tumor Necrosis Factor alpha

TRAIL : Tumor-Necrosis-Factor Related Apoptosis Inducing Ligand

UCP1 : Protéine Découplante

VLDL : Very Low Density Lipoprotein ou lipoprotéines de très basse densité

Résumé

L'incidence du surpoids et de l'obésité est en constante augmentation au niveau mondial. Cette pandémie est non seulement associée au développement du diabète de type 2, de l'hypertension artérielle, des pathologies cardio-vasculaires, mais aussi à des complications hépatiques telles que la Non-Alcoholic SteatoHepatitis (NASH) qui peut évoluer vers la cirrhose et/ou le carcinome hépatocellulaire.
La sleeve gastrectomie (SG) est une opération bariatrique qui consiste à réduire le volume de l'estomac en réalisant une gastrectomie longitudinale. L'hypothèse que d'autres mécanismes indépendants de la perte de poids sont impliqués dans l'amélioration des complications hépatiques et métaboliques de l'obésité après SG a été émise. Dans un premier temps un modèle murin de SG a été mis au point et puis l'effet de la SG chez des souris C57Bl/6J soumis à un régime High Fat Diet pendant 33 semaines a été étudié chez trois groupes d'animaux : groupe *SG*, groupe *sham pair fed* (SPF, animaux alimentés avec la même quantité de nourriture consommée par les animaux du groupe SG) et groupe *sham* (animaux alimentés ad libitum). A J23 de la SG les animaux SG, SPF et Sham pesaient en moyenne 79±7,1 %, 85,15± 3 % et 99,25±4 % de leur poids initial respectivement (*p<0,001*). La prise alimentaire a été identique entre le groupe SG (1,88 g/j) et groupe SPF (1,88 g/j) et significativement inférieure au groupe sham (4,5 g/j) (*p< 0,05*). Le test de tolérance au glucose montrait une amélioration de l'insulinorésistance des animaux SG à J23. L'aire sous la courbe du groupe SG, SPF et Sham à J20 était de 5925, 11903,1 et 13140 g*min/ml respectivement (*p< 0,001*). Au niveau hépatique les animaux SG montraient une diminution significative de la stéatose (SG vs. SPF, *p< 0,05*; SPF vs. Sham, *p<0.01*). Il existe donc des mécanismes améliorant les complications hépatiques et métaboliques de l'obésité qui sont en partie indépendants de la réduction de l'apport calorique.

Dans le second volet nous avons étudié l'évolution à long terme des lésions hépatiques liées à la NASH chez des patients obèses morbides avec une NASH prouvée histologiquement (NAS score ≥ 5) lors de la chirurgie bariatrique (gastric bypass sur anse en Y (LRYGB)). Dix patients (9 femmes/ 1 homme) de la cohorte prospective du Service de Chirurgie Digestive du CHU de Nice avec un âge moyen de 46,4 ± 4 ans ont été inclus dans cette étude. La deuxième biopsie a été réalisée à une médiane de 57 mois [Q1 ; Q3 : 44; 79] après le LRYGB. La perte de poids moyenne était de –13,3[–15.9; –9.3] points de l' IMC lors du suivi et tous les patients avaient perdu > 50% de leur poids en excès. La rémission du syndrome métabolique et du diabète a été observée chez 71,6 % et 100 % des patients respectivement. Le NAS score a été amélioré chez tous les patients (amélioration de la stéatose chez 100 %, de l'inflammation chez 90,9 %, de la souffrance hépatocytaire chez 90,9 % et de la fibrose chez 72,7 % des patients). Le taux sérique moyen du fragment clivé de la cytokératine 18 (M30), marqueur de l'apoptose hépatocytaire, était à 442,98 ± 92,17 U/l avant le LRYGB en faveur d'une souffrance hépatocytaire. Au moment du suivi le taux sérique du M30 était significativement baissé à 226,81 ± 8,6 U/L (*p<0,018*). Le LRYGB a permis une amélioration à long terme des lésions hépatocytaires liées à la NASH chez les patients obèses morbides. L'amélioration post-opératoire de la souffrance hépatocytaire corrèle avec la baisse du taux sérique du M30.

Introduction

Généralités

L'obésité

L'obésité est un problème de santé publique majeur et la prévalence des sujets obèses morbides ne cesse d'augmenter. En 1997 l'étude ObEpi avait recensé 1,5 % de français avec un indice de masse corporelle (IMC) ≥ 35 kg/m² et en 2012 le chiffre avait triplé ("ObEpi-Roche, enquête épidémiologique de référence sur l'évolution de l'obésité et du surpoids en France," n.d.) (Fig. 1).

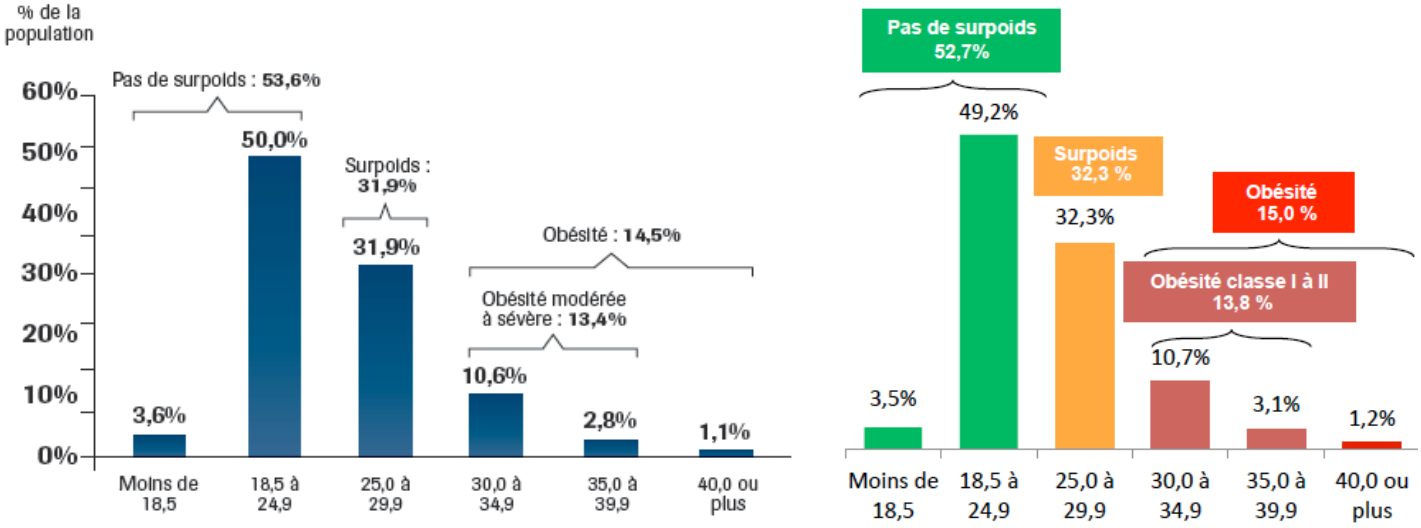


Figure 1. Répartition de la population française en fonction de son niveau d'IMC en 2009 et 2012 respectivement (ObEpi-Roche).

La gravité de cette épidémie est liée aux comorbidités associées à l'obésité (Must et al., 1999):

- l'insulino-résistance (IR) et le diabète de type 2 (DT2),
- l'hypertension artérielle (HTA),
- les dyslipidémies,
- le syndrome des apnées du sommeil (SAS),
- les arthropathies,

- les stéatopathies métaboliques (NAFLD, non-alcoholic fatty liver disease).

Les comorbidités sont responsables d'une diminution de l'espérance et de la qualité de vie. Il est établi que la perte de poids est primordiale dans le traitement de l'obésité et de ses comorbidités. La chirurgie bariatrique est le seul moyen thérapeutique qui peut permettre une perte de poids stable à long terme améliorant ainsi les comorbidités, l'espérance et la qualité de vie (Sjöström et al., 2004).

Le syndrome métabolique (tableau 1)

Le syndrome métabolique (SM) associe des anomalies morphologiques, physiologiques et biochimiques qui évoluent en fonction du temps, prédisposant le sujet atteint à l'athérosclérose et à ses complications. Actuellement, il est défini par trois sur les cinq éléments suivants : un tour de taille ≥ 94 cm chez les hommes européens et ≥ 80 cm chez les femmes européennes; une hypertriglycéridémie; un taux faible du HDL-cholestérol; une HTA; une hyperglycémie ou un DT2 (Alberti et al., 2009) (Tableau 1). La NAFLD est considérée comme la manifestation hépatique du SM (Ratziu et al., 2010).

L'insulinorésistance (IR) est le dénominateur commun des anomalies. Elle prédispose au DT2, aux dyslipidémies et à un état pro-inflammatoire.

	Homme	Femme
Tour de taille	> 94 cm	> 80 cm
HDL cholestérol	< 0,4 g/L	< 0,5 g/L
Taux de triglycérides	> 1,5 g/L	
Pression artérielle	Systolique > 130 mmHg Diastolique > 85 mmHg	
Taux de glucose	> 1,01 g/L	

Tableau 1 Définition du syndrome métabolique.

L'insulinorésistance

L'IR est définie par la baisse de la réponse cellulaire ou tissulaire à l'insuline en présence d'une concentration normale d'insuline. L'IR joue un rôle central dans le développement de la stéatose (Lewis and Mohanty, 2010) car elle est responsable d'une accumulation de graisses au niveau du foie. De même, l'IR est l'une des principales causes du SM (Bastard et al., 2001). L'IR précède souvent le DT2. En cas d'IR, d'une part la néoglucogenèse et la glycogénolyse hépatique ne seront plus inhibées par l'insuline, d'autre part la glycogénogenèse et lipogenèse seront augmentées.

Les cytokines inflammatoires altèrent la signalisation insulinique par une phosphorylation inactivatrice des résidus sérine/thréonine des récepteurs à l'insuline (IRS). Les AG ou leurs métabolites sont également capables de contrecarrer la cascade de signalisation de l'insuline directement dans le muscle, le foie et le TA et ce en aval du récepteur. Ils activent une cascade de sérine/thréonine kinases conduisant à la phosphorylation des IRS sur des résidus sérine et thréonine. La phosphorylation de ces résidus perturbe la phosphorylation des résidus tyrosine et l'activation de la

phosphoinositide 3-kinase (PI3K). Cela altère le reste de la cascade de signalisation avec en conséquence, entre autres, une diminution de la translocation des transporteurs du glucose (Shulman, 2000).

L'inflammation chronique du TA blanc, caractérisée par une infiltration macrophagique, peut aussi contribuer à l'IR (Weisberg et al., 2003), de même que le stress oxydatif. En effet, certains AG augmentent les espèces réactives de l'oxygène (ROS, reactive oxygen species) notamment par des réactions de peroxydation.

Le tissu adipeux blanc

Le rôle initial du TA est une protection de l'organisme à travers le stockage des acides gras libres (AGL), diminuant ainsi l'exposition des autres organes à la toxicité des AGL. En cas d'apport trop excessif de graisses, on observe une hypertrophie des adipocytes. Cela est associé à une modification de l'expression génique des adipocytes (Lumeng and Saltiel, 2011) conduisant à une infiltration macrophagique du TA. Les AGL activent les récepteurs Toll-like (TLR)-4 au niveau des macrophages et des adipocytes activant de cette manière des cascades inflammatoires dont celle du nuclear factor-kappa B (NF-κB) (Yuan et al., 2001).

En effet, le TA est maintenant reconnu comme un organe endocrinien à part entière car les adipocytes et la fraction stromale du TA sécrètent divers médiateurs dont les adipocytokines et les cytokines (TNF-α, IL). Celles qui jouent un rôle important dans la NAFLD sont l'adiponectine, la leptine, le TNF-α et l'IL-6. L'expression de ces médiateurs est étroitement liée à l'obésité centrale. Ils jouent un rôle important dans la modulation de la voie de signalisation de l'insuline et des cascades inflammatoires. Ces deux

phénomènes sont primordiaux dans l'accumulation de graisses au niveau hépatique, mais aussi dans la progression de la stéatohépatite (Powell et al., 2010).

L'adiponectine est une adipocytokine anti-inflammatoire dont les concentrations circulantes sont diminuées lorsque l'IMC, la masse grasse et les TG augmentent (Cheung and Sanyal, 2010). Elle est connue pour son effet anti-athérogène, anti-inflammatoire et anti-diabétogène. L'hypoadiponectinémie augmente la stéatose hépatique et induit le stress du réticulum endoplasmique (RE) et une inflammation hépatique (Purushotham et al., 2009). Au final l'adiponectine exercerait des effets insulino-sensibilisateurs dans le muscle, le foie et le TA via une régulation fine du métabolisme glucidique et lipidique.

La leptine stimule la β-oxydation des AG. Sa sécrétion est proportionnelle à l'accumulation de TG au niveau des adipocytes en cas d'obésité. L'augmentation des taux plasmatiques stimule la libération d'AG et diminue leur stockage au niveau des adipocytes. Elle stimule également l'inflammation et la fibrogenèse.

L'IL-6 et le TNF-α sont les adipocytokines dont le rôle est central dans l'évolution de l'inflammation hépatique (Park et al., 2010).

Au cours de l'obésité, il existe une inflammation de bas grade avec une augmentation des concentrations plasmatiques de nombreux marqueurs de l'inflammation (Khan et al., 2014). Etant surexprimé dans le tissu adipeux (TA) de différents modèles animaux d'obésité (Hotamisligil et al., 1993), le TNF-α (Tumor Necrosis Factor-α) est considéré comme une des molécules faisant le lien entre inflammation et obésité. En effet, la voie de stress de la protéine 1 activatrice de la c-Jun terminal kinase active la sécrétion du TNF-α par les macrophages.

Le tissu adipeux brun

La fonction du TA brun est la thermogenèse, principalement en relation avec le maintien de la température corporelle à 37°C. Il joue un rôle important dans la thermogenèse adaptative qui est la dépense énergétique provoquée par des changements environnementaux comme le froid, un excès de prise alimentaire, une infection microbienne ou virale. Mais il semble aussi être impliqué dans la thermogenèse obligatoire ou induite par l'alimentation (Ricquier, 2012). Le TA brun est un organe capable de brûler les graisses et peut s'opposer à leur stockage.

Les dépôts de TA brun sont richement vascularisés, contrairement au TA blanc. De plus, les adipocytes bruns sont directement innervés par des fibres orthosympathiques capables de libérer la noradrénaline. L'adipocyte brun est caractérisé par la présence d'un très grand nombre de mitochondries, ce qui indique que ces cellules ont une forte capacité d'oxydation des substrats (Nicholls and Locke, 1984). La thermogenèse du TA brun est médiée par la protéine découplante UCP1, une protéine capable de découpler le fonctionnement de la chaîne respiratoire de la synthèse d'adénosine triphosphate (ATP). Le rôle du TA brun dans l'obésité reste à être élucidé. Plusieurs études ont démontré une corrélation inverse entre la prévalence de TA brun détectable et l'IMC (Cypess et al., 2009).

Des travaux récents ont permis de localiser le TA brun chez l'humain adulte dans la région cervicale (région sus-claviculaire et muscles sternocléidomastoïdiens) (Cypess et al., 2009).

Circuits neurohormonaux et satiété

L'hypothalamus joue un rôle central dans la régulation de la prise alimentaire et du poids corporel. Parmi la quarantaine de noyaux hypothalamiques, le noyau arqué (NA) joue un rôle fondamental dans le contrôle de l'homéostasie énergétique par l'expression de plusieurs neuropeptides. Il existe au sein du NA deux populations de neurones: les neurones à NPY (neuropeptide Y) et à AgRP (Agouti Related Peptide) et les neurones à POMC (pro-opio-mélanocortine) et à CART (Cocaine & Amphetamine-Related Transcript). Le NPY et l'AgRP sont des neuropeptides orexigènes qui stimulent la prise alimentaire et diminuent les dépenses énergétiques. La synthèse et la libération du NPY dans l'hypothalamus est inhibée par l'insuline et la leptine et est stimulée par la ghréline et les corticoïdes. Le principal neuropeptide anorexigène du NA est l'α-MSH (α-Melanocyte-Stimulating Hormone). Ce peptide est clivé à partir de son précurseur, la pro-opiomélanocortine (POMC) (Korner and Leibel, 2003).

Les stéatopathies métaboliques

Définition

Le terme de NAFLD regroupe différents degrés d'atteintes hépatiques :

La stéatose

La stéatose est définie par une surcharge de triglycérides (TG) dans le foie sous forme de vacuoles lipidiques au niveau des hépatocytes. Plus de 5 % des hépatocytes doivent être atteints. Il s'agit surtout d'une stéatose macro-vacuolaire qui est classée en trois grades en fonction du pourcentage d'hépatocytes atteints : **0**: < 5%; **1**: 5 à 33%; **2**: 34 à 66%; **3**:> 66%. Elle se développe initialement dans les zones péri-centrolobulaires. (Fig 2)

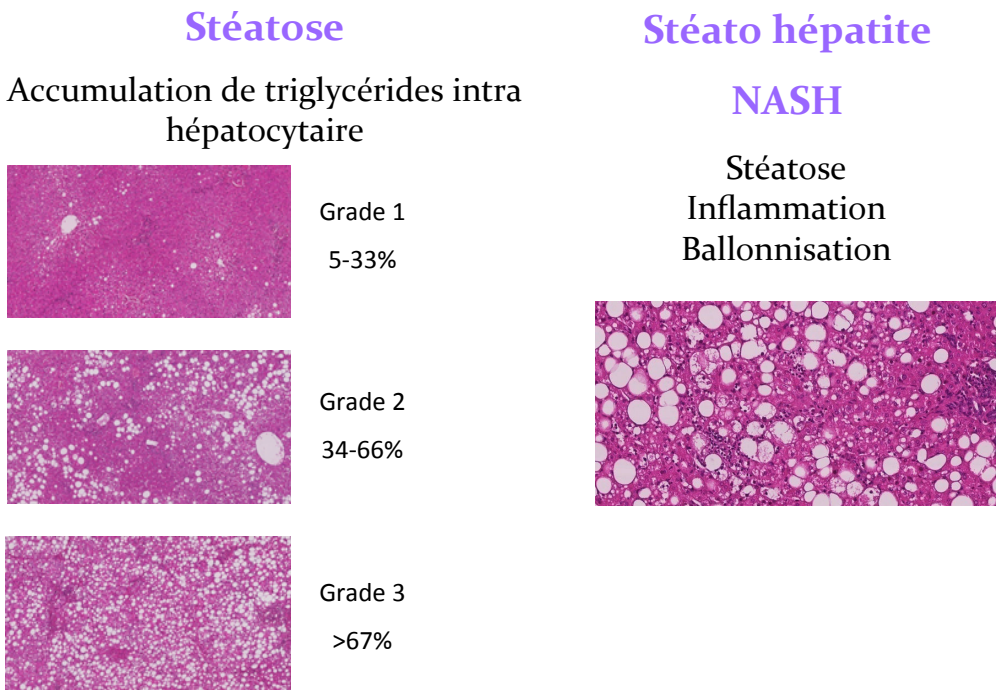


Figure 2. Aspects histopathologiques des NAFLD et NASH.

La stéatohépatite

La stéatohépatite (Non Alcoholic Steato Hepatitis, NASH) est caractérisée par une stéatose associée à un infiltrat inflammatoire et à une lésion de l'hépatocyte, (ballonisation de la cellule et mort cellulaire) (Brunt, 2001). L'infiltrat lobulaire inflammatoire est constitué en majorité de cellules inflammatoires mononuclées (lymphocytes et macrophages) (Yeh et Brunt 2014). La ballonisation de l'hépatocyte est définie par une augmentation de la taille de la cellule ainsi qu'une clarification de son cytoplasme. Les corps de Mallory peuvent se développer au sein de ces hépatocytes ballonisés. La ballonisation et l'inflammation sont également classées selon les critères définis par Brunt (Brunt, 2000). Trois grades sont proposés pour la ballonisation selon le nombres d'hépatocytes atteints (**0**: aucun ; **1**: quelques ; **2**: nombreux) et quatre grades pour l'inflammation selon le nombre de foyers inflammatoires observés au grandissement 200 (**0**: aucun; **1**: < 2; **2**: 2 – 4; **3**: > 4).

Le score NAS

La somme du grade des ces lésions (stéatose, ballonisation, inflammation) permet d'établir le score NAS (NAFLD Activity Score) de 0 à 8. Le diagnostic de stéatohépatite est éliminé par un score inférieur à 2, tandis qu'il es affirmé par un score supérieur à 5 (Kleiner et al. 2005).

La fibrose

La fibrose est considérée comme une conséquence de la NASH, elle n'est pas incluse dans le score NAS. Elle se développe initialement dans les sinus des zones péri-centro-lobulaires et elle est classée en quatre grades : **1** : fibrose sinusoïdale péri-centrolobulaire, (**a**) discrète; (**b**) modérée; (**c**) péri-portale; **2** : fibrose sinusoïdale, péri-centrolobulaire et péri-portale; **3** : présence de pont fibreux; **4** : cirrhose.

Degré d'activité de la NASH: degré = score total: S + L + B (range 0–8)					
Stéatose	S score	Inflammation lobulaire	L score	Ballonisation hépatocytaire	B score
< 5%	0	Aucune	0	Aucune	0
5–33%	1	< 2	1	Peu de cellules ballonisées	1
34–66%	2	2–4	2	Nombreuses cellules ballonisées	2
> 66%	3	> 4	3		
Stade de la fibrose de la NASH				Stade	
Aucune				0	
Légère, fibrose périsinusoïdale zone 3				1a	
Modérée, fibrose périsinusoïdale zone 3				1b	
Fibrose portale/periportale uniquement				1c	
Fibrose périsinusoïdale et portale/périportale Zone 3				2	
Ponts fibreux (porto-portaux)				3	
Cirrhose				4	

Tableau 2. Système de notation histologique de la NASH selon le Clinical Research Network (Kleiner et al, 2005)

Le diagnostic de la NAFLD est toujours histologique et nécessite donc par définition une biopsie hépatique.

Epidémiologie

Les stéatopathies métaboliques ou Non Alcoholic Fatty Liver Disease (NAFLD) sont devenues la cause la plus fréquente d'hépatopathie chronique dans les pays occidentaux (Armstrong et al., 2012). Leur prévalence est difficile à évaluer, mais un tiers des adultes américains seraient atteints d'une NAFLD. En Europe, les chiffres varient de 20 à 30 % (Loomba and Sanyal, 2013). Des études histologiques ont retrouvé chez des sujets sains, potentiels donneurs de foie vivants en vue d'une transplantation hépatique, une prévalence de NAFLD de 12-18 % en Europe et de 27-38 % aux Etats-Unis (Minervini et al., 2009). L'obésité est un facteur de risque connu de la NAFLD. Chez le sujet obèse morbide, la prévalence de la NAFLD et de la NASH est de 70% et 30% respectivement

(Bedossa et al., 2012)(Machado et al., 2006). Dans les populations à risque, l'étude européenne DIONYSOS a retrouvé une NAFLD chez 25% des sujets avec un IMC <25 kg/m^2, chez 67% avec un IMC entre 25–29 kg/m^2 et chez 94% des sujets obèses avec un IMC ≥30 kg/m^2 (Bellentani et al., 2004). Chez les sujets diabétiques la prévalence de NAFLD est de 40 – 70% (Argo and Caldwell, 2009). Chez les patients opérés d'une chirurgie bariatrique la prévalence de la NAFLD peut atteindre 90 %. Au cours du bilan en vue de la chirurgie bariatrique jusqu'à 5% des patients peuvent être atteints d'une cirrhose non suspectée (Boza et al., 2005)(Chalasani et al., 2012). Une étude prospective sur 328 personnes (âge moyen de 54 ans) basée sur un questionnaire, une échographie abdominale et une biopsie hépatique (chez les sujets dont l'échographie était positive) a montré une prévalence de la NAFLD de 46% et une prévalence de la NASH de 12,2% (Williams et al., 2011). Il y avait 40 sujets atteints d'une NASH, soit 29,9% des sujets ayant un foie stéatosique à l'échographie. L'étude confirme que la NAFLD et la NASH sont plus souvent présentes chez les hommes, obèses ou en surpoids, avec des antécédents d'HTA et de DT2. Les patients atteints de NAFLD consommaient plus fréquemment des repas «au fast food» et avaient une activité physique moindre (Williams et al., 2011).

L'enjeu de cette pathologie est majeur. Aux Etats-Unis les cirrhoses d'origine métabolique sont devenues la troisième indication de transplantation hépatique (Agopian et al., 2012). Le pourcentage de patients transplantés pour NASH augmente chaque année. Il est passé de 1,2% en 2001 à 9,7% en 2009 (Charlton et al., 2011).

Les 3 premières causes de mortalité chez les patients atteints d'une NAFLD sont dans l'ordre les maladies cardio-vasculaires, le cancer et les pathologies hépatiques (Adams et al., 2005).

Histoire naturelle de la NAFLD

La NAFLD est généralement asymptomatique, mais ces lésions hépatiques peuvent évoluer vers la fibrose (Ekstedt et al., 2006) (Pais et al., 2011) et la cirrhose. Il est estimé que 10 à 30 % des sujets qui présentent une NASH développe une cirrhose dans les 10 ans à venir (Argo et al., 2009)(Argo and Caldwell, 2009)(Matteoni et al., 1999). Le risque de carcinome hépatocellulaire (CHC) est également augmenté (Baffy et al., 2012), indépendamment du fait qu'il y ait une cirrhose NASH sous-jacente ou non. En effet, le diabète, l'obésité et le syndrome métabolique sont des facteurs de risque indépendants du développement du CHC (Paradis et al., 2009). Sorensen *et al.* ont montré dans une étude menée sur le registre national danois de 1977 à 1993 que le risque de développer un cancer primitif sur une NAFLD était élevé avec un risque relatif standardisé de 4,4 (Sørensen et al., 2003). Dans une étude cas-contrôle japonaise, 34 patients ayant une NASH et un CHC ont été comparés à 348 patients ayant une NASH sans CHC. Les résultats ont montré que l'âge et le grade de la fibrose étaient des facteurs de risque importants pour le développement d'un CHC (Hashimoto et al., 2009).

Physiopathologie (Figure 3)

L'accumulation de graisses au niveau du foie est due à

1) un afflux augmenté d'AGL provenant de la lipolyse du tissu adipeux (TA) viscéral et sous-cutané et/ou d'un apport augmenté de graisses alimentaires

2) une diminution de la β-oxydation des AG

3) une augmentation de la lipogenèse hépatique *de novo*

4) une diminution de la sécrétion hépatique de VLDL (very low density lipoprotein ou lipoprotéines de très basse densité) (Fabbrini et al., 2008).

En postprandial, en cas de IR, les adipocytes libèrent des AGL en excès, alors que dans des conditions physiologiques la lipolyse devrait être inhibée. L'hydrolyse des TG circulants est également augmentée. Ceci a pour conséquence que les AG qui affluent au niveau hépatique sont préférentiellement estérifiés et stockés sous forme de TG. Mais leur sécrétion au sein de VLDL est inhibée.

Les AGL sont eux-mêmes cytotoxiques (Alkhouri et al., 2009) en provoquant des lésions hépatocytaires médiées par le Tumor Necrosis Factor alpha (TNFα) et en provoquant la formation de radicaux libres.

Les enzymes impliquées dans ces voies (glucokinase et L-pyruvate kinase pour la glycolyse ; acétyl-CoA carboxylase et fatty acid synthase pour la lipogenèse) sont régulées en partie au niveau transcriptionnel par des facteurs de transcription comme SREBP-1c (sterol regulatory element-binding protein) et ChREBP (carbohydrate responsive element-binding protein) qui induisent la lipogenèse suite à leur activation respectivement par le glucose et par l'insuline (Robichon et al., 2008). Ainsi, en cas d'hyperinsulinémie et de DT2, l'hyperglycémie active le ChREBP tandis que l'hyperinsulinémie induit le SREBP-1c. L'action simultanée et synergique de ces deux facteurs de transcription conduit à l'activation transcriptionnelle des gènes de la lipogenèse.

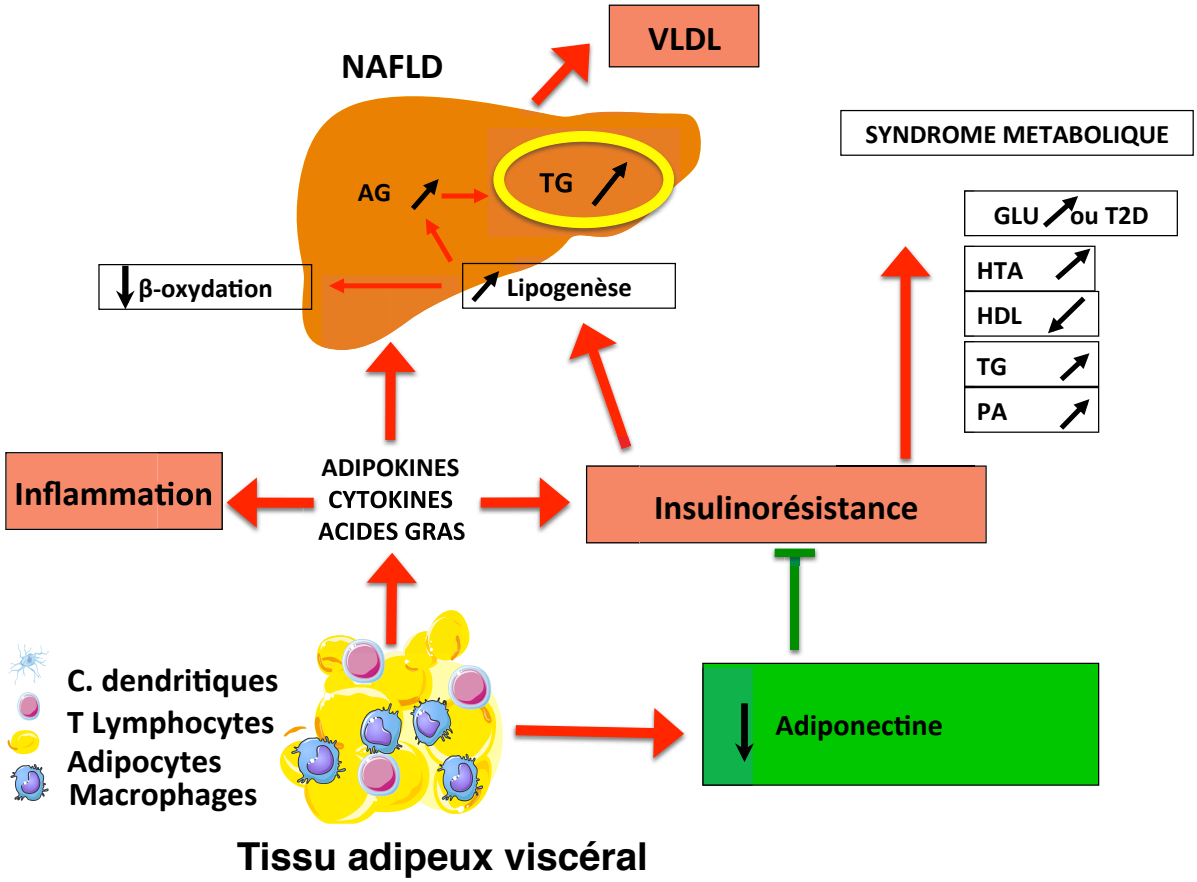


Figure 3. Origine de la stéatose hépatique. L'accumulation d'acides gras (AG) dans le foie peut être due à un apport exogène à partir des AG libres dus à la lipolyse augmentée dans le tissu adipeux (TA) viscéral dans le cas d'une alimentation riche en graisse ou d'une insulinorésistance.

Les oméga 3

Les AG polyinsaturés (AGPI) peuvent avoir un rôle pro-inflammatoire ou anti-inflammatoire. Ceci dépend de leur structure. Les AGPI oméga-6, tels que l'acide linoléique ou l'acide arachidonique, sont des précurseurs des eicosanoïdes pro-inflammatoires (thromboxane A2, leucotriène, prostaglandines) (Calder, 2006). Mais, au contraire, les AGPI oméga-3, tels que l'acide α-linolénique (ALA), l'acide docosahexaénoïque (DHA) et l'acide eicosapentaénoïque (EPA), jouent un rôle anti-inflammatoire important. L'ALA est retrouvé dans les huiles végétales, surtout l'huile de lin, et le DHA et EPA sont retrouvés dans les poissons gras et l'huile de poisson. Les AGPI oméga-3 rentrent en compétition avec les AGPI oméga-6, ce qui peut diminuer les voies

pro-inflammatoires et pro-thrombotiques. Les DHA et EPA régulent les facteurs de transcription (peroxisome proliferator-activated receptor (PPAR)-α, PPAR-γ, SREBP-1, ChREBP) qui contrôlent les voies de signalisation impliquées dans le métabolisme lipidique. En effet, les AGPI oméga-3 sont des activateurs puissants de PPAR-α qui stimulent différents gènes jouant un rôle dans l'oxydation des AG et qui inhibent les gènes pro-inflammatoires tels que TNF-α et interleukine (IL)-6. De plus, ils activent le PPAR-γ augmentant ainsi l'oxydation des AG et améliorant la sensibilité à l'insuline (Di Minno et al., 2012). Par ailleurs, les AGPI oméga-3 inhibent l'expression de SERBP-1 et ChREBP, ce qui diminue la lipogenèse et la glycolyse hépatique (Sekiya et al., 2003).

L'immunité

L'immunité innée consiste en une série de systèmes de défense non spécifiques et représente la première barrière de défense contre des dangers exogènes et endogènes. Les mécanismes de l'immunité innée comprennent des «pathogen-associated molecular patterns» (PAMP) et des «damage-associated molecular patterns» (DAMP) qui sont reconnus par 4 classes de récepteurs (pattern-recognition receptors (PRR)) dont les TLR. Au niveau du foie, l'activation du système immunitaire inné joue un rôle primordial dans l'homéostasie, la régénération hépatique, mais aussi dans la pathogenèse de certaines maladies. Les TLR sont exprimés à la surface des cellules de Kupffer, des cellules hépatiques stellaires (CHS), des cellules épithéliales biliaires, des cellules sinusoïdales et des cellules dendritiques (Seki and Brenner, 2008).

Une modification des PAMP et des voies de signalisation à travers les TLR est responsable de la pathogenèse de différentes maladies hépatiques, dont la NASH. Plus précisément, une surexpression du TLR-4 activé par le lipopolysaccharide (LPS) a été retrouvée dans un modèle animal de NASH. Ainsi, des souris non mutées, alimentées

avec une nourriture normale, ont développé une stéatose hépatique après l'administration de LPS à petite dose (Cani et al., 2007). Ces travaux entre autres suggèrent que l'inflammation hépatique dépend des voies de signalisation médiées par le TLR-4 au niveau des cellules de Kupffer et des CHS.

Dans un foie atteint de NASH, on observe une infiltration du foie par des cellules inflammatoires. Dans un foie sain, les cellules T «natural killer» (NKT) se trouvent au niveau des sinusoïdes hépatiques et jouent un rôle de communication entre les systèmes immunitaires inné et acquis. Le rôle exact des NKT dans la pathogenèse de la NAFLD reste débattu (Gao et al., 2009). La stéatose est associée à une diminution du nombre de cellules NKT hépatiques proportionnellement au degré de stéatose (Kremer et al., 2010). Par contre, dans un foie atteint de NASH, on observe une augmentation du nombre de cellules NKT hépatiques (Tajiri et al., 2009).

La mort cellulaire

La mort cellulaire est un élément central dans le développement d'une NAFLD. Il existe plusieurs types de mort cellulaire : l'apoptose, l'autophagie, la nécroptose ou la nécrose.

L'apoptose est une mort cellulaire programmée qui atteint surtout les hépatocytes en cas de NAFLD ou de NASH. Au sein des hépatocytes, les AGL peuvent induire une perméabilisation lysosomiale et une dysfonction mitochondriale qui mènent à l'apoptose de la cellule (Ricchi et al., 2009). Les corps apoptiques ainsi relâchés sont des activateurs important des CHS responsables de la fibrose (Canbay et al., 2004). Chez les sujets atteints de NASH, une augmentation de l'apoptose hépatocytaire a été mise en évidence. Celle-ci est liée à différents récepteurs activant la voie extrinsèque de l'apoptose. En effet, l'expression de la protéine Fas est plus augmentée chez les patients atteints de NASH que chez les patients présentant une stéatose (Feldstein et al., 2004).

L'autophagie est un mécanisme cellulaire catabolique où certains composants intracellulaires sont engloutis et subissent une dégradation protéolytique. L'autophagie permet de maintenir le métabolisme en cas de rupture d'apports énergétiques et de prévenir l'accumulation de toxines lors d'un stress métabolique. Ainsi elle permet la survie de la cellule. L'autophagie a un rôle de protection contre la NAFLD car elle permet une dégradation des lipides hépatiques. En effet, en cas de surcharge lipidique, l'autophagie augmente au niveau de l'hépatocyte. Mais en cas de NAFLD le processus d'autophagie est mis en échec. Ceci peut être dû à une exposition chronique à un excès de lipides et à une exposition à des AG saturés qui inhibent l'autophagie (Schneider and Cuervo, 2014)(Lavallard and Gual, 2014).

La nécrose est une mort cellulaire définie comme accidentelle, non programmée. Elle est généralement due à une hypoxie aiguë ou une ischémie. Une cellule en apoptose nécessite de l'ATP et lorsqu'elle est en manque la cellule passe d'un processus d'apoptose à un processus de nécrose (Hotchkiss et al., 2009). La nécroptose est une « nécrose cellulaire programmée » induite par des stimuli externes en réponse à l'activation des «récepteurs de mort» par leurs ligands respectifs (TNF-α, tumor-necrosis-factor related apoptosis inducing ligand (TRAIL) ...). Des travaux récents ont mis en évidence son rôle potentiel dans l'évolution de la NAFLD à la NASH et enfin la fibrose (Gautheron et al., 2014).

Le microbiote

Le microbiote intestinal est constitué en majorité de Firmicutes et Bactéroïdetes qui représentent 90% des organismes. Les autres familles telles que les Protéobactéries, le Lactobacillaceae et les Mollicutes sont présents en quantité négligeable (Lozupone et al., 2012). L'étude du microbiote a mis en évidence que la distribution des microorganismes chez le sujet obèse est modifiée par rapport au sujet normal. En effet, la balance est en faveur des Firmicutes et la flore est moins diversifiée (Zhang et al., 2009)(Turnbaugh et al., 2006).

Afin d'étudier le lien entre le microbiote et l'obésité, des microorganismes ont été transférés de sujets obèses à des souris «germ-free» ou à des sujets minces. Dans les suites, le receveur présentait le même phénotype métabolique que le donneur (Fei and Zhao, 2013)(Vrieze et al., 2012).

Les mécanismes impliqués sont les suivants :

- le microbiote produit des molécules telles que l'acétate et propionate qui peuvent activer des voies métaboliques à travers les récepteurs épithéliaux intestinaux.
- l'altération de la perméabilité intestinale augmente la translocation bactérienne et aboutit à une inflammation chronique. Les PAMP (LPS) activent les TLR (4 et 9) sur population cellulaire T. L'activation des TLR des cellules de Kuppfer active la sécrétion de cytokines pro-inflammatoires qui induisent une inflammation dans le foie. Le LPS intervient dans la fibrogenèse en activant le récepteur TLR4 des cellules étoilées et des cellules endothéliales sinusoïdales (Seki et al., 2007)(Jagavelu et al., 2010).

Il a été montré que l'inflammation chronique induit un phénotype insulino-résistant qui est un élément clé dans le développement de la NAFLD (Shen et al., 2013)(Anstee et al., 2013).

La relation entre le microbiote intestinal et la NAFLD est connue depuis plus de 20 ans. Elle a été mise en évidence chez les patients présentant une pullulation bactérienne qui développent une NAFLD (Lichtman et al., 1991). En cas de pullulation bactérienne il existe un afflux accru d'endotoxines au niveau du sang portal. Ces endotoxines activent le système immunitaire du foie, notamment les NKT (Kubes and Mehal, 2012)(Tordjman et al., 2008)(Aron-Wisnewsky et al., 2013).

Mécanismes

Initialement, en 1998, a été proposée la théorie des «deux coups» (Day and James, 1998). Le premier «coup» est la dégénérescence graisseuse des hépatocytes due à l'afflux élevé d'AGL au niveau hépatique. Celui-ci est lié à l'apport alimentaire important, à la libération accrue à partir des tissus adipeux et à la synthèse *de novo* renforcée par l'IR. Cette stéatose rendrait les hépatocytes plus sensibles au second «coup» dû au stress oxydatif mitochondrial, au stress du RE, aux cytokines inflammatoires et aux adipokines relarguées par le TA. Cela aboutirait à la constitution de la stéatohépatite et à l'apparition de fibrose. Actuellement, cette théorie est remise en question et remplacée par la théorie à «multiples coups parallèles» (Tilg and Moschen, 2010). Les AGL, non stockés sous la forme de TG, ont une toxicité hépatique car ils augmentent le stress oxydatif mitochondrial, le stress du RE et activent directement la production des cytokines inflammatoires (TNF-α, IL-6). Les cytokines inflammatoires engendrent également l'apoptose qui entretient l'inflammation chronique du parenchyme hépatique. Les hépatocytes apoptotiques activent les cellules de Kupffer. Ces macrophages résidents du foie sont responsables d'une part de l'augmentation de l'inflammation, et d'autre part de la progression de la fibrose.

La β-oxydation mitochondriale est la voie oxydative des acides gras dans les conditions physiologiques normales. Chez les sujets atteints d'une NAFLD ces voies sont inhibées et sont la source principale de radicaux libres (Powell et al., 2010; Cheung and Sanyal, 2010). De nombreuses études fondamentales et cliniques ont montré le lien qui existe entre la sévérité de l'atteinte hépatique et le degré de stress oxydatif (Cheung and Sanyal, 2010). Il existe une augmentation des marqueurs sériques du stress oxydatif et une diminution des molécules anti-oxydantes chez les sujets atteints d'une NASH. Le taux de ces marqueurs est corrélé avec la sévérité de l'atteinte hépatique et l'IR (Cheung and Sanyal, 2010). En revanche, le TNF-α et l'IL-6 diminuent l'expression de l'adiponectine dans les adipocytes humains (Ruan and Lodish, 2003).

Traitement

La prise en charge des patients atteints d'une NAFLD comprend le traitement de la pathologie hépatique mais aussi des pathologies métaboliques associées que sont l'obésité, les dyslipidémies, l'IR et le DT2. Elle a pour but de prévenir la progression des lésions hépatiques induites par la lipotoxicité et/ou d'en obtenir la rémission.

Les mesures hygiéno-diététiques

La première approche est de corriger l'IR et de réduire la masse grasse en prenant des mesures hygiéno-diététiques avec une modification du comportement alimentaire et une augmentation de l'activité physique. Une diminution des apports en sucres rapides et graisses saturées permet une réduction de la stéatose et du taux sérique des transaminases (Huang et al., 2005). Une étude randomisée a comparé une modification du mode de vie importante (régime, modification du comportant alimentaire et 200 minutes d'activité physique modérée par semaine pendant 48 semaines) à seulement

une éducation thérapeutique (Promrat et al., 2010). La perte de poids était de 9,3 % dans le groupe intensif contre 0,2 % dans le groupe éducation thérapeutique seule. Cela a mené dans le groupe intensif à une amélioration de la stéatose, la nécrose et l'inflammation, mais non pas de la fibrose. D'autres études ont rapporté des résultats équivalents montrant l'effet bénéfique d'une perte de poids sur la NAFLD et la NASH. La réduction de la stéatose est proportionnelle à la perte de poids. Une perte de poids de 3-5% est nécessaire pour améliorer la stéatose, tandis qu'une perte de poids de 10 % est nécessaire pour améliorer la nécro-inflammation (Chalasani et al., 2012).

Les médicaments

Plusieurs médicaments ont été proposés dans la prise en charge de la NAFLD. Les agents sensibilisateurs à l'insuline, dont la metformine, ont été étudiés. La metformine diminue le taux sérique des transaminases, mais aucune étude n'a pu démontrer une amélioration nette de la stéatose et stéato-hépatite sur le plan histologique (Shields et al., 2009). Les thiazolidinediones (pioglitazone et rosiglitazone) ont également été proposées pour le traitement de la NAFLD. Plusieurs études ont montré une amélioration du taux sérique des transaminases et de l'histologie. L'étude PIVENS, un essai multicentrique, contrôlé, randomisé, a montré que la pioglitazone permet une résolution de la NASH chez 47 % des patient contre 0,21 % des patients traités par placebo (Sanyal et al., 2010). Par contre, malgré leur efficacité, les thiazolidinediones ne sont pas recommandées car elles exposent à un risque accru de maladies cardiovasculaires. La rosiglitazone a été retiré du marché en Europe.

La vitamine E est un anti-oxydant et a été étudiée dans le traitement de la NAFLD. Il est admis que la vitamine E est associée à une diminution du taux des transaminases ainsi qu'une amélioration de la stéatose, de l'inflammation et de la ballonisation hépatocytaire

chez les patients atteints de NASH. L'étude PIVENS a montré qu'une administration de 800 UI par jour de α-tocophérol pendant 96 semaines permettait une diminution de 2 points NAS chez 42 % des patients *versus* 0,19 % des patients traités par placebo. Mais il persiste des controverses sur la sûreté de la vitamine E éventuellement associée à une augmentation de la mortalité (Miller et al., 2005) et du cancer de la prostate chez les hommes (Klein et al., 2011). Chez les patients NASH le ratio oméga-3/oméga-6 des AG polyinsaturés ingérés est diminué. Quelques études ont montré que l'augmentation de l'apport en oméga-3 pourrait améliorer l'état métabolique et histologique hépatique (Tanaka et al., 2008). Une méta-analyse portant sur 9 études a confirmé que la supplémentation en AGPI oméga-3 d'origine marine avait un effet bénéfique sur la stéatose hépatique (Parker et al., 2012).

Les probiotiques sont des micro-organismes vivants qui, lorsqu'ils sont ingérés en quantité suffisante, exercent des effets positifs sur la santé. Les deux probiotiques les plus étudiés sont Bifidobacterium et Lactobacillus. Des études expérimentales ont démontré une amélioration de la NAFLD chez les souris *ob/ob* avec une diminution de la stéatose et des taux sériques des transaminases (Li et al., 2003). L'application chez l'humain reste difficile, car l'ingestion de probiotiques est très faible par rapport au microbiote endogène.

En conclusion, il n'existe à ce jour aucun traitement efficace et sans effet secondaire majeur pour la NAFLD et NASH.

Traitement chirurgical (chirurgie bariatrique)

La chirurgie bariatrique a tout naturellement trouvé sa place dans la prise en charge de la NAFLD car la majorité des patients opérés présente une NAFLD/NASH.

Les indications de chirurgie bariatrique en France ("http://www.has-sante.fr/portail/upload/docs/application/pdf/2009-04/obesite_-_prise_en_charge_chirurgicale_chez_ladulte_-_synthese_des_recommandations.pdf," n.d.) suivent les recommandations de la conférence de consensus du National Institute of Health, 1991 ("Gastrointestinal surgery for severe obesity," 1991). Elles comprennent :

- obésité morbide (IMC ≥ 40 kg/m^2) résistante au traitement médical et exposant le patient à des complications graves qui ne peuvent être contrôlées par le traitement spécifique
- obésité avec IMC entre 35 et 40 kg/m^2 associée à des comorbidités menaçant la vie ou le pronostic fonctionnel : affection cardiovasculaire, maladie ostéo-articulaire instable, désordres métaboliques sévères non contrôlés par un traitement intensif.

Dans chaque cas, l'indication ne peut être envisagée que chez des patients ayant eu accès à une prise en charge médicale spécialisée pendant au moins six mois, comprenant également des approches complémentaires (diététique, activité physique, prise en charge des difficultés psychologiques, traitement des complications). Le patient doit consentir par écrit à un suivi médical prolongé.

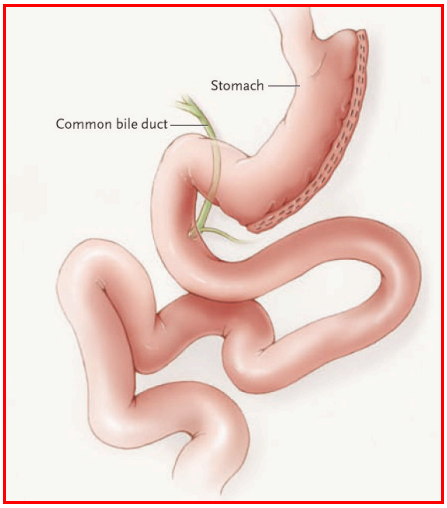
La chirurgie bariatrique est actuellement le seul traitement de l'obésité morbide qui permet d'obtenir une perte de poids significative et l'amélioration ou la rémission de comorbidités liées à l'obésité à long terme (Sjöström et al., 2007).

Selon une enquête de Buchwald *et al.* en 2011, actuellement, quatre interventions sont couramment pratiquées : le court-circuit gastrique (RYGBP) dans 46.6 % des cas, la sleeve gastrectomie (SG) dans 27.8 %, l'anneau gastrique ajustable (AGB) dans 17.8 % et la dérivation bilio-pancréatique avec switch duodénal (SD) dans 2.2 % (Buchwald and Oien, 2013a).

L'AGB est une intervention purement restrictive qui consiste à mettre en place un anneau gonflable en silicone au niveau du fundus gastrique créant ainsi une poche gastrique de 15-30 ml. L'anneau est relié à un boitier sous-cutané qui permet d'ajuster la pression que l'anneau exerce sur la paroi gastrique pour ajuster le niveau de restriction alimentaire du patient.

La seconde intervention restrictive, la SG, est une gastrectomie partielle le long de la petite courbure gastrique calibrée par un tube de calibre variable entre 36 – 46 Fr. La SG agit en réduisant la capacité gastrique et de ce fait le volume du bol alimentaire ingéré.

Le RYGBP reste l'opération de référence en chirurgie bariatrique. Il a une composante restrictive due à la création d'une poche gastrique de 30 à 40 ml au niveau de la petite courbure gastrique et d'une anastomose gastro-jéjunale calibrée à 10 mm ainsi qu'une composante malabsorptive grâce à un court-circuit intestinal sur une anse alimentaire en Y de 150 cm de longueur (Figure 4).

A 

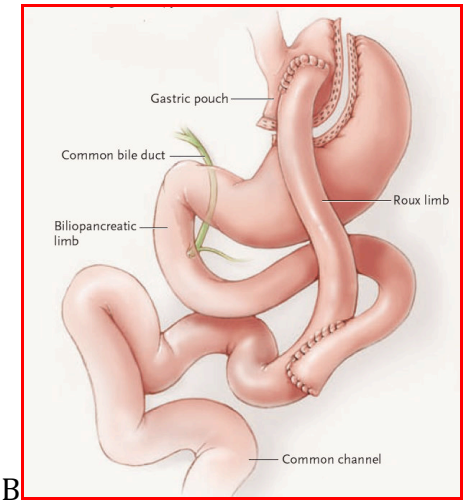
B 

Figure 4. A. La Sleeve gastrectomie (SG), B. Le court-circuit gastrique en Roux-en-Y (RYGBP)

La dernière intervention, de moins en moins pratiquée, est le SD composé d'une partie restrictive, la SG, et une partie malabsorptive obtenue par une dérivation bilio-pancréatique: une anse alimentaire est anastomosée au premier duodénum et l'anse bilio-pancréatique est anastomosée à l'iléon à 100 cm de la valvule iléo-caecale. Cette dernière opération est très peu pratiquée (2,2 % des procédures au niveau mondial, (Buchwald and Oien, 2013a).

Les résultats en terme de perte pondérale ont été rapportés dans plusieurs séries et méta-analyses. Selon O'Brien *et al.*, les résultats à long terme avec un pourcentage de perte de poids en excès (%PPE) sont de 47 % à 15 ans pour l'AGB (O'Brien et al., 2013). Higa *et al.* rapporte un %PPE de 57% à 10 ans pour le RYGBP (Higa et al., 2011) et Hess *et al.* un %PPE de 75% à 10 ans pour le SD (Hess et al., 2005). La SG est une intervention plus récente dont les résultats à plus de 10 ans ne sont pas encore publiés. Néanmoins Sarela *et al*. rapporte un %PPE de 68 ans à 8 ans (Sarela et al., 2012).

La sleeve gastrectomie

L'intervention la plus pratiquée en France a longtemps été le RYGBP, mais depuis 2012, c'est la SG ("French National Hospital Database(Programme De Médicalisation des Systèmes d'Information – PMSI).

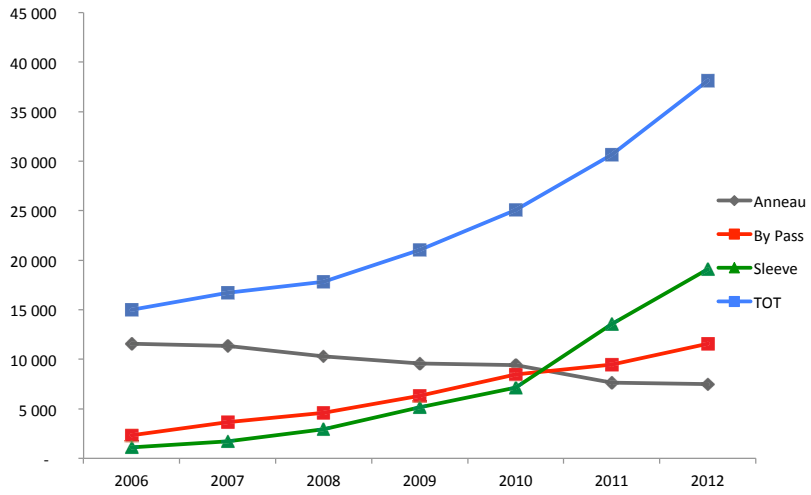


Figure 5. Les données PMSI de la chirurgie bariatrique en France de 2006 à 2012.

Initialement la SG était une des deux composantes du SD décrite par Marceau *et al.* (Marceau et al., 1998). Afin de réduire le risque opératoire chez le patient super-obèse (IMC > 50 kg/m^2), une stratégie en deux temps a été proposée (Regan et al., 2003) avec dans un premier temps la réalisation de la SG et dans un second temps une procédure malabsorptive telle que le RYGBP ou le SD. Rapidement, la SG a été décrite comme procédure à part car elle permettait une perte pondérale > 50 % du poids en excès et une amélioration des pathologies associées (Iannelli et al., 2008)(Deitel et al., 2008). L'avantage de la SG par rapport au RYGBP est sa simplicité technique, l'absence de court-circuit intestinal et le respect de l'anatomie permettant l'accès endoscopique du tube digestif. Le tendon d'Achille de cette intervention est la fistule haute au niveau de la lignée d'agrafage. Le taux de cette complication redoutable était estimé à 3-5% en 2009 (Gagner et al., 2009). Depuis, le taux de fistules a diminué et le taux de complications post-opératoires est maintenant comparable au RYGBP (Colquitt et al., 2014).

L'estomac

L'estomac est également un organe endocrinien dont les cellules sécrétantes se situent essentiellement au niveau du fundus. La ghréline, hormone peptidique, régule la sécrétion de l'hormone de croissance et a un effet orexigène lié à l'activation des récepteurs hypothalamiques et pituitaires (Ghigo et al., 2005). Elle est sécrétée au niveau des cellules X/A-like des glandes oxyntiques. La régulation à long terme du taux de ghréline circulant est liée au poids corporel. En effet son taux est élevé lorsque la balance énergétique est négative (Cummings et al., 2002), par exemple lors d'un exercice chronique ou d'une anorexie (Wisse et al., 2001). En revanche le taux de ghréline est abaissé lorsque la balance énergétique est positive, notamment chez le sujet obèse (Shiiya et al., 2002). La régulation immédiate du taux de ghréline est liée à la prise alimentaire : sa concentration plasmatique augmente avant et diminue après chaque repas (Cummings et al., 2002). Elle a l'effet inverse des peptides tels que la cholécystokinine (CCK), le peptide tyrosine tyrosine 3-36 (PYY) et le glucagon like peptide 1 (GLP-1). Ces facteurs de satiété sont tous les trois impliqués dans la régulation à court-terme de la prise alimentaire par leur action au niveau du système nerveux central (SNC). Le GLP-1 est sécrété par les cellules endocrines intestinales en réponse à un repas. Il augmente la sécrétion d'insuline en activant des récepteurs spécifiques au niveau des cellules β pancréatiques. Le PYY est sécrété par les cellules L neuro-endocrines intestinales et son taux circulant dépend des aliments ingérés. Il est impliqué dans la sensation de satiété et dans la régulation du poids corporel à long terme (Karra and Batterham, 2010).

La SG, outre la restriction, provoque aussi une action supplémentaire par diminution du taux de ghréline en phase post-opératoire, ainsi qu'une élévation des taux de PYY et GLP-1 à l'origine des effets sur le traitement du DT2. En effet Peterli *et al.* ont montré que les changements hormonaux survenaient déjà quelques jours après la chirurgie. Cela suggère qu'il existe d'autres mécanismes que la perte pondérale pour améliorer les pathologies métaboliques associées à l'obésité (Peterli et al., 2009). Par ailleurs Langer *et al.* ont trouvé un taux de ghréline diminué de manière significative chez dix patients qui ont eu une SG à un et six mois post-opératoires, comparé à dix patients ayant eu un AGB (Langer et al., 2005).

Mécanismes impliqués dans la résolution de la NAFLD après la chirurgie bariatrique

Les mécanismes des procédures malabsorptives sont complexes et dépendent de la longueur de l'intestin court-circuité et de la modulation des peptides neuro-endocrines sécrétés. Ces derniers agissent à travers plusieurs voies de signalisation dont la sécrétion augmentée de PYY, hormone anorexigène, suite au contact rapide des aliments à la muqueuse de l'iléum. La sécrétion des incrétines (GLP 1, GLP 2) impliquées dans l'axe entéro-insulaire est également augmentée.

Les mécanismes impliqués dans l'amélioration ou la résolution de la NAFLD peuvent être séparés en deux groupes: ceux directement liés à la perte de poids et ceux indépendants de la restriction calorique et donc non liés à la perte pondérale.

La restriction calorique

La restriction gastrique est associée à une restriction calorique et à une diminution d'apport en sucres rapides et en graisses responsables de la dyslipidémie et de la

stéatose hépatique. La perte pondérale est associée à une augmentation de la sensibilité à l'insuline qui diminue la libération d'AGL du TA. La diminution de l'inflammation du TA entraîne une diminution des médiateurs de l'inflammation (adipokines et cytokines) et une augmentation du taux plasmatique d'adiponectine. Ceci améliore la sensibilité à l'insuline.

L'inflammation et l'insulinorésistance

La SG et le RYGBP induisent une diminution de la sécrétion post-prandiale de GLP-1 qui permet une diminution de la stéatose hépatique grâce à différentes actions dont la stimulation de la sécrétion de l'insuline, la libération moindre du glucose hépatique et la diminution de la résistance à l'insuline du foie et du tissu adipeux. Le GLP-1 active également les gènes PPARα/γ qui augmentent la β-oxydation hépatique des AG, l'exportation des lipides et la sensibilité à l'insuline. L'inflammation hépatique est diminuée en inhibant l'expression de TNFα, IL-6, IL-1β, et monocyte chemotactic protein 1 (MCP-1) (Tran and Gual, 2013).

Le RYGBP diminue l'IR en augmentant l'adiponectine et en modifiant la flore intestinale secondairement aux changements de la production biliaire et de l'afflux des nutriments. La nouvelle flore intestinale, avec moins de Firmicutes et plus de Proteobacteries, modifie le métabolisme énergétique: le métabolisme des oligosaccharides permet une production plus importante d'AG à courtes chaines (propionate, acétate, etc…) qui stimulent l'expression des médiateurs clés de la sensibilité de l'insuline.

Résultats

Premier volet

Au début de ce travail de thèse, je me suis intéressée aux effets de la chirurgie bariatrique sur les comorbidités liée à l'obésité, notamment le diabète, et aux mécanismes impliqués. Les modèles murins ont été introduits dans ce domaine afin de mieux comprendre au niveau cellulaire, moléculaire et génétique les observations faites chez les sujets obèses opérés (Ashrafian et al., 2010). La réalisation du bypass jéjunoiléal chez le rat a permis de différencier l'obésité génétique (Zucker *fa/fa*) et l'obésité induite après réalisation d'une lésion au niveau de l'hypothalamus ventro-médial des rats. Les animaux rendu obèses par une lésion hypothalamique ont diminué leur ingesta jusqu'à atteindre le poids des contrôles sham (Sclafani et al., 1978). Dans un autre modèle animal, il a été montré qu'après la réalisation d'une gastro-entéro-anastomose dérivant le duodénum et le jéjunum proximal chez la souris, l'homéostasie glucidique était améliorée par l'augmentation du GLP-1 après l'administration de glucose, la néoglucogenèse intestinale et la détection du glucose par le «gut glucose transporter-2 hepatoportalsensoring» (Troy et al., 2008).

La sleeve gastrectomie (SG) n'a pas évolué à partir d'un modèle animal, mais a été développée à partir d'une opération qui existait déjà, la dérivation bilio-pancréatique avec switch duodénal (SD) (Gagner et al., 2009). Cette opération a connu un essor particulièrement important et rapide après son introduction récente en pratique clinique courante. Aujourd'hui la SG est devenue la procédure bariatrique la plus réalisée en France avec environ 18,000 procédures en 2012 ("French National Hospital Database(Programme De Médicalisation des Systèmes d'Information – PMSI).

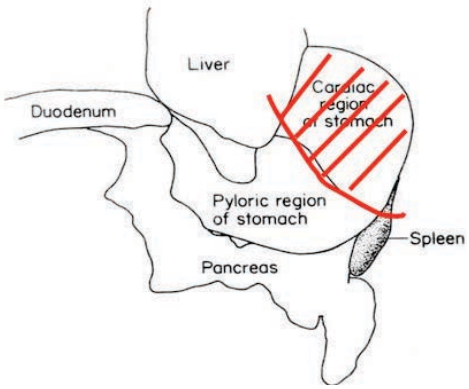
Lors du début de mon travail de master 2 en 2009, il n'existait pas de modèle animal de la SG. Les mécanismes responsables de l'évolution de l'insulinorésistance (IR), de la stéatose hépatique et de la perte de poids après cette opération n'avaient pas encore été étudiés dans le modèle animal. Le but était de donc de mettre au point un modèle animal pour tester l'hypothèse que des mécanismes autres que la restriction alimentaire soient impliqués dans la perte de poids, dans la rémission de l'IR et de la stéatose hépatique. Le modèle animal est le seul qui permet d'obtenir des contrôles adéquats tels que les animaux «sham pair fed» (SPF) pour vérifier cette hypothèse. Les animaux SPF sont des animaux qui reçoivent une nourriture qualitativement et quantitativement identique à celle des animaux qui ont eu l'intervention bariatrique étudiée. Difficilement reproductible chez l'humain, ce modèle SPF offre un groupe contrôle pour la composante restrictive de l'intervention bariatrique étudiée.

La mise au point du modèle murin.

Dans un premier temps, nous avons mis au point la technique chirurgicale adaptée à l'estomac murin. En effet, l'anatomie de l'estomac murin diffère de celle de l'humain car le tissu de l'estomac pylorique et celui de l'estomac cardial ne sont pas les mêmes. L'estomac pylorique est glandulaire alors que l'estomac cardial est uniquement constitué d'une fine membrane. Lorsque la résection gastrique est réalisée avec une pince de viscéro-synthèse à partir du fundus vers l'angle de His une partie de l'estomac cardial reste en place. Nous avons constaté au début de notre expérience que l'exérèse de l'estomac cardial doit être effectuée de manière très précise car cette partie de l'estomac tend à se dilater (Fig 6C). Lopez *et al.* ont fait la même constatation dans leur modèle animal (Lopez et al., 2009). L'évolution du poids chez les animaux non obèses montre que ces animaux récupèrent rapidement la perte de poids due à la SG sans pour

autant rejoindre le poids des animaux du groupe contrôle (résultats du Master 2, AS Schneck). Par ailleurs, les animaux s'adaptent rapidement à une prise alimentaire qui n'est pas significativement différente de celle des animaux de contrôle. Par contre, les animaux rendus obèses avec un régime riche en graisses (High Fat Diet 60%) ont une perte pondérale après SG significativement différente par rapport aux animaux minces. Différents articles parus récemment ont décrit un modèle réalisé avec la persistance de l'estomac cardial (Schlager et al., 2011). En particulier un modèle chez le rat a été décrit avec l'utilisation d'une agrafeuse mécanique linéaire (Stefater et al., 2010). Compte tenu l'anatomie gastrique chez le rongeur, l'agrafage ne permet pas l'exérèse complète de l'estomac cardial. Un travail préliminaire de mise au point du modèle nous a montré que si une partie de l'estomac cardial est laissée en place, une dilatation se produit très rapidement en 2 mois, comme cela a été constaté à la nécropsie. Dans nos travaux préliminaires, cet effet anatomique correspondait à une reprise de poids initialement perdu (*cf* Lettre à l'éditeur de Iannelli *et al.* en réponse de l'article de Yin *et al.* (Yin et al., 2011)). L'opération que nous avons mise au point consiste alors dans un premier temps à une résection complète de l'estomac cardial, puis dans un second temps d'une réduction de volume de l'estomac glandulaire.

A.



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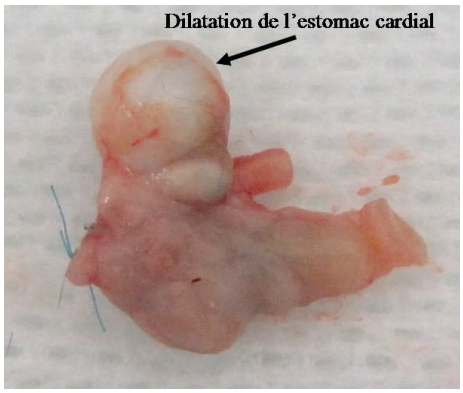

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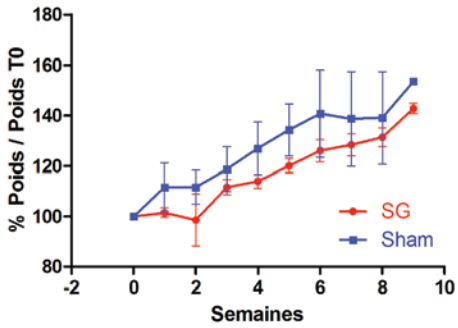

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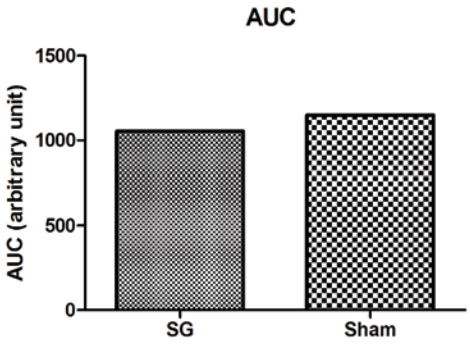

Figure 6 A. Anatomie de l'estomac murin avec la limite de résection de la région cardiale et fundique de l'estomac. B. Estomac murin à 2 mois de la chirurgie. A gauche, estomac des animaux contrôles, à droite l'estomac après SG. C. Dilatation de l'estomac cardial à 2 mois de la SG. D. Evolution du poids chez les souris du groupe SG et Sham en pourcentage du poids initial (T0). E. Prise de poids totale sur 2 mois dans les 2 groupes (ns).

Après le modèle chirurgical, le deuxième problème a été de choisir un modèle d'obésité qui se rapproche de l'obésité due à un excès calorique. Dans un premier temps, nous voulions utiliser des animaux génétiquement obèses tels que les souris *ob/ob*. Ces animaux offrent l'avantage d'être disponibles sur le marché et d'avoir des lésions de

stéatohépatite. Malheureusement ces animaux sont particulièrement fragiles et ne résistent pas au stress de la chirurgie, ce qui mène à une mortalité post-opératoire élevée.

Le modèle animal a un rôle important dans la recherche des mécanismes métaboliques de la perte de poids, car il existe beaucoup de limites d'ordre méthodologique et éthique pour réaliser ces expériences chez l'humain. Nous avons donc choisi un modèle de régime riche en graisses (high fat diet (HFD)) qui se rapproche beaucoup du modèle de l'obésité occidentale chez l'humain (Stylopoulos et al., 2005)(Fraulob et al., 2010).

Notre modèle animal a montré que la SG permet une perte de poids supérieure à celle que l'on peut obtenir avec la restriction alimentaire isolée. D'autres mécanismes que la restriction alimentaire sont impliqués dans la perte pondérale ainsi que dans l'amélioration de l'IR et de la stéatose hépatique. Nous avons aussi pu démontrer que la SG s'associe à une diminution du ratio de poids du pancréas, du tissu adipeux épididymal (équivalent du tissu adipeux viscéral chez l'humain) et inguinal sur le poids corporel. La diminution du tissu adipeux épididymal est accompagnée d'une diminution de l'infiltration de celui-ci par les cellules T activées et d'une augmentation du nombre de cellules T régulatrices anti-inflammatoires. Il existe également une augmentation du ratio du tissu adipeux brun sur le poids corporel. Ces données montrent qu'après SG, plusieurs mécanismes sont responsables de la perte de poids et de l'évolution des comorbidités en plus de la simple restriction alimentaire.

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Effects of sleeve gastrectomy in high fat diet-induced obese mice: respective role of reduced caloric intake, white adipose tissue inflammation and changes in adipose tissue and ectopic fat depots

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Abstract
Background Sleeve gastrectomy (SG) has become a popular bariatric procedure. The mechanisms responsible for weight loss and improvement of metabolic disturbances have still not been completely elucidated. We investigated the effect of SG on body weight, adipose tissue depots, glucose tolerance, and liver steatosis independent of reduced caloric intake in high-fat-diet-induced obese mice.
Methods C57BI/6 J mice fed a high fat diet (45 %) for 33 weeks were divided into three groups: sleeve gastrectomy (SG, 13 mice), sham-operated ad libitum fed (SALF, 13 mice) and sham-operated pair fed (PFS, 13 mice). The animals were humanely killed 23 days after surgery.
Results In SG mice, food intake was reduced transiently, but weight loss was significant and persistent compared to controls (SG vs. PFS, $P < 0.05$; PFS vs. SALF, $P < 0.05$). SG mice showed improved glucose tolerance and lower levels of liver steatosis compared with controls (area under the curve, SG vs. PFS, $P < 0.01$; PFS vs. SALF, $P < 0.05$) (liver steatosis, SG vs. PFS, $P < 0.05$; PFS vs. SALF, $P < 0.01$). This was associated with a decrease in the ratios of the weight of pancreas, epididymal and inguinal adipose tissues to body weight, and an increase in the ratio of brown adipose tissue weight to body weight. Epididymal adipose tissue was also infiltrated by fewer activated T cells and by more anti-inflammatory regulatory T cells. Serum levels of fasting acyl ghrelin were still significantly decreased 3 weeks after surgery in SG mice compared to PFS mice ($P < 0.05$).
Conclusions Reduced white adipose tissue inflammation, modification of adipose tissue development (brown vs. white adipose tissue), and ectopic fat are potential

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mechanisms that may account for the reduced caloric intake independent effects of SG.

Keywords Bariatric surgery · Glucose tolerance · Morbid obesity · Sleeve gastrectomy · Weight loss

Sleeve gastrectomy (SG), first reported as the restrictive part of the biliopancreatic diversion with duodenal switch [1], rapidly gained wide consensus in the bariatric surgical community because of its straightforward surgical technique. It preserves the pylorus and lacks intestinal bypass, which makes the upper digestive tract accessible to endoscopic exploration [2]. Furthermore, the weight loss obtained with SG has been shown to be comparable to that reported for Roux-en-Y gastric bypass, not only in the short term but also beyond 5 years [3]. This has made SG a legitimate stand-alone bariatric procedure [3].

SG consists of vertical gastrectomy over an intraluminal calibration bougie that reduces by about 80 % the capacity of the stomach and results in a dramatic reduction in food intake. However, it has been shown that SG is associated with a decrease in the circulating levels of fasting ghrelin, the orexigenic hormone mainly secreted by the gastric fundus mucosa [4], and postprandial intestinal peptides such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which influence appetite and food intake [5]. The reported short-term results for SG and Roux-en-Y gastric bypass suggest a comparable effect on type 2 diabetes [6, 7]. Furthermore, although the metabolic effects of SG can be at least partly explained by a reduction in the fat mass occurring after surgery, other mechanisms may be responsible for improvement in glucose tolerance, such as a decrease in the low-grade systemic inflammatory state linked to obesity [8]. Taken together, these results indicate that the mechanisms leading to the loss of weight and metabolic changes that follow SG cannot be explained solely by the reduced caloric intake induced by a reduction in the gastric capacity.

We tested the hypothesis that reduced caloric intake alone is not sufficient to account for the effects of SG on body weight, glucose tolerance, and liver steatosis in high fat diet (HFD)-induced obese mice. We also investigated the role of inflammation of adipose tissue on metabolic disturbances linked to obesity.

Materials and methods

Animals and study design

Two-month-old male C57BL/6 J mice (Janvier) acclimated to our animal facilities under a 12/12-h light/dark cycle at a temperature of 21 ± 2 °C were fed ad libitum a HFD (45 kcal % fat, 35 kcal % carbohydrate, 20 kcal % protein) (D12451; Research Diets) and a fructose sweetened beverage (3 %) for 32 weeks. At 40 weeks of age, mice underwent the surgical procedures as described below. All experiments were performed according to the institutional guidelines for the care and use of laboratory animals under a license issued by the local ethical committee. Mice were assigned to one of three groups. Group 1 ($n = 13$) consisted of sham-operated, ad libitum-fed mice (SALF). In this group, mice had a laparotomy only with ad libitum access to food and water after surgery. Group 2 ($n = 13$) consisted of mice that had the SG. These mice also had ad libitum access to food and water after surgery. The group 3 mice ($n = 13$) were sham-operated pair-fed (PFS) mice. These mice had a laparotomy only with access to the same amount of food as their counterparts in group 2. Before surgery, mice were deprived of food for 8 h. Mice were fed the same HFD after surgery for the duration of the study.

Operative technique

Anesthesia was induced and maintained throughout the procedure with intraperitoneal injection of ketamine (150 mg/kg) and xylazine (20 mg/kg). Preoperatively, 20 mg/kg ceftriaxone (Sandoz) was administered, and 6 mg/ml paracetamol (Macopharma) was added to the drinking water after surgery. Mice were placed on a heating pad to avoid hypothermia, and the abdomen was disinfected before a 2-cm midline laparotomy was performed. The model for SG in mice has been previously validated in other studies [9, 10]. Our model is a modified version of what has previously been reported. The mouse stomach contains two well-defined areas, a nonglandular forestomach and a glandular stomach that is connected to the duodenum. Ghrelin is produced in the distal glandular stomach. The forestomach was resected first, and the glandular stomach was then closed with a 6-0 polypropylene (Prolene; Ethicon Inc.) running suture. To complete the SG to the glandular stomach, a metallic clip (Premium Surgiclip II; Covidien Surgical) was placed on the glandular stomach parallel to the lesser curvature (midway between the lesser and greater curvature), and a vertical gastrectomy was performed along the clip that was used to guide a 6-0 polypropylene running suture. The abdominal wall was closed with Monocryl 4-0 (Ethicon Inc.) (continuous suturing). The skin was closed with Monocryl 3-0 (Ethicon Inc.) (intracutaneous continuous suturing). In the sham-treated groups (SALF and PFS), the stomach was mobilized, and the time of surgery was then extended for the same duration required to perform the SG to mimic surgery-related stress and trauma. After surgery, animals

were housed individually and subcutaneous fluids (1 ml of NaCl 0.9 %; Laboratoire Aguettant) were administered for the first postoperative day. Animals were given free access to a fructose-sweetened beverage 6 h after surgery and a HFD the day after surgery. Two days after surgery, the animals were housed five per cage.

Food intake and body weight measurement

Food intake was monitored every day for each cage from 1 week before surgery and then throughout the study period. PFS mice were given the same amount of food as the SG mice. SALF mice were given free access to food and water. For body weight measurement, mice were weighted individually daily at 6 a.m. from 1 week before surgery and throughout the study period. All animals were humanely killed 23 days after surgery. Each animal underwent necropsy immediately after death, and the epididymal (EAT), brown (BAT), and inguinal adipose tissues (IAT) were collected, weighed (in the case of EAT a sample was further processed as indicated below), and snap frozen at −80 °C. The liver and pancreas were also collected. A sample was sent for histology, and the remaining tissue was snap frozen at −80 °C.

Histopathological assessment of steatosis

Liver samples were fixed in 4 % neutral-buffered formaldehyde solution and embedded in paraffin for pathological evaluation after hematoxylin and eosin staining. Results are expressed as percentages and represent the mean number of hepatocytes with macrovesicular steatosis. Histological examination was performed in a blinded fashion by the same pathologist.

Intraperitoneal glucose tolerance test (IGTT)

Mice were fasted for 8 h with free access to water. Conscious mice received an intraperitoneal injection of a glucose solution (1 g/kg body weight; 250 mg/ml) and blood glucose levels were determined before (baseline) and every 30 min for 180 min using a glucometer optium (Xceed; Abbott).

Serum transaminases, fasting ghrelin

Serum fasting ghrelin concentrations were assessed using a rat/mouse ghrelin (active) ELISA (Millipore Corporation) according to the manufacturer's protocol. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) serum concentrations were measured with an Olympus AU5400 (Olympus France) automatic analyzer.

Preparation of the stromal vascular fraction of adipose tissue

White epididymal adipose tissue pads were removed and the stromal vascular fraction was immediately purified as previously described [11]. Briefly, adipose tissue pads were cut into small pieces and rinsed in a buffer containing 120 mM NaCl, 4 mM KH_2 PO_4, 1 mM $MgSO_4$, 750 µM $CaCl_2$, 10 mM $NaHCO_3$ and 30 mM HEPES pH 7.4. Explants were incubated at 37 °C for 30 min in 15 ml of the above buffer supplemented with 1 % BSA, 280 mM glucose and 15 mg of type 1 collagenase (Worthington Biochemical Corporation). Adipocytes were then collected by filtration and floatation. The stromal vascular fraction was collected by centrifugation for 5 min at 750 g.

Antibodies and flow cytometric analysis

Hamster antibodies against mouse CD3 (clone 145-2C11) and rat antibodies against mouse CD44 (clone IM7) and FoxP3 (clone FJK-16s) were purchased from Becton–Dickinson or eBioscience. For intracellular staining, the FoxP3 staining buffer set (eBioscience) was used according to the manufacturer's instructions. Flow cytometry was performed on a FACS-Canto and analyzed using FACS-Diva version 6.0 software (BD-Bioscience).

RNA isolation and quantitative real-time PCR

Hypothalami were dissected and stored at −80 °C. Total mRNA was isolated according the Chowynski method using a Fast Prep apparatus (Q-Biogene). Two micrograms of total RNA were denatured at 65 °C for 10 min and incubated for 1 h at 42 °C in presence of 2.5 mM dNTP, 100 U Superscript II (Invitrogen) using 0.5 µg oligo(dT) primer in a total volume of 20 µl, followed by inactivation for 15 min at 70 °C. A negative control lacking RT was also performed in each assay (NRT). Real time PCR was performed from reverse transcribed cDNA samples for relative amounts of mRNA levels for the genes of interest. Quantitative real time PCR was performed in a Light Cycler 480 apparatus (Roche Diagnostics) using qPCRTMMastermix Plus for SYBR Green I reagent (Eurogentec) as described by the manufacturer. Primers were designed using Primer Express 1.5 software (Applied Biosystems). mPOMC-F: AGTGCCAGGACCTCACCA; mPOMC-R: CAGCGAGAGGTCGAGTTTG; mNPY-F: CCGCTCTGCGACACTACAT; mNPY-R: TGTCTCAG GGCTGGATCTCT; mAgRP-F: CCCAGAGTTCCCA GGTCTAAGTCT; mAgRP-R: CACCTCCGCCAAAGCT TCT. mGAPDH-F: GAACATCATCCCTGCATCC; mGA PDH-R: CCAGTGAGCTTCCCGTTCA. Five microliters of the RT or NRT mixture was added to 1× Sybr Green

PCR buffer containing 5 mM $MgCl_2$, dNTPs including dUTP, uracyl-*N* glycosylase, SYBR Green I, and Hot Goldstar DNA polymerase in a total volume of 25 µl. PCR cycling was performed at 95 °C for 15 s and 60 °C for 1 min for a total of 40 cycles. Real-time PCR was performed to amplify mouse POMC, NPY, AgRP, and GAPDH mRNA. For each assay, the PCR was performed in duplicate to determine the relative quantities of target genes and GAPDH amplicons.

Statistical analysis

The Kruskal–Wallis test was used for the comparison of more than two study groups. If the Kruskal–Wallis test was significant, then a Mann–Whitney *U* test was used for comparison between groups for statistical significance. All values are expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed by NCSS 2007 software. $P < 0.05$ was considered to be significant.

Results

Body weight, food intake, ghrelin serum level, and expression of melanocortin system neuropeptides

Five animals died immediately after surgery within 6 h. The death was attributed to anesthesia because no anomaly was found at necropsy.

No differences between the three groups of mice with respect to body weight (SALF 48.4 ± 2.5 g vs. SG 46.7 ± 2.3 g vs. PFS 48.4 ± 4.9 g, $P = 0.335$) and daily food intake (SALF 2.2 ± 0.12 g vs. SG 2.6 ± 0.1 g vs. PFS 2.4 ± 0.15 g, $P = 0.15$) were observed before surgery. SG mice showed a significant weight loss compared to SALF mice, as expected (SG 36.9 ± 3.9 g vs. SALF 48.1 ± 4.2 g, $P < 0.05$), but also compared to PFS mice (SG 36.9 ± 3.9 g vs. PFS 41.3 ± 4.9 g, $P < 0.05$) (Fig. 1A, B). On average, SG mice consumed spontaneously significantly less chow per day for the first 2 weeks than SALF mice and reached the control mice on the third week (Fig. 1C, D). In agreement with this, both the gene expression of the neuropeptide Y (NPY) and Agouti-related peptide (AgRP) in the hypothalamus arcuate nucleus, which increase feeding and decrease energy expenditure, were not different in SG mice compared to control mice ($P = 0.799$ and $P = 0.799$, respectively). Likewise, the gene expression of the pro-opiomelanocortin (POMC) gene, which decreases appetite and increases energy expenditure, was not different among the three groups (Fig. 1E) at the end of the experiment ($P = 0.551$).

However, the serum levels of fasting acyl ghrelin were still significantly decreased 3 weeks after surgery in SG mice compared to PFS mice (SG 101.5 ± 13.7 pg/ml vs. PFS 298.1 ± 68.8 pg/ml, $P < 0.042$). Taken together, these data indicate that the loss of weight that follows SG cannot be explained exclusively by the reduced caloric intake of SG.

Glucose tolerance

We then evaluated the impact of SG on glucose tolerance. Although the three groups of mice were intolerant to glucose before surgery (Fig. 2A), SG mice and PFS mice showed significantly better glucose tolerance on day 15 compared with the baseline glucose time course as shown by the IGTT, with lower 60-, 90-, and 120-min peak levels (Fig. 2A, B) ($P < 0.05$) and a lower mean area under the curve (AUC) (SG 5925 ± 1083.7 mg/dl [min] vs. PFS 11903.1 ± 818.8 mg/dl [min] vs. SALF 13140 ± 1668.3 mg/dl [min]; SG vs. PFS, $P < 0.01$; SG vs. SALF, $P < 0.01$) (Fig. 2C). As expected, glucose tolerance did not improve in SALF mice (mean AUC, $P = 0.895$). SG mice showed a significantly lower mean AUC after IGTT ($P < 0.01$) and lower 60-, 90-, and 120-min peak levels ($P < 0.05$) compared to PFS mice (Fig. 2A–C), indicating that food restriction was not sufficient to account for the improvement in glucose tolerance observed in SG mice.

Weight of the pancreas and body fat

Fat accumulation in the pancreas and expansion of adipose tissue, inflammation play an important role in alterations to glucose homeostasis. Interestingly, the mean pancreas/body weight ratio was significantly lower in SG mice compared to control groups (SG 0.27 ± 0.06 vs. PFS 0.44 ± 0.03, $P = 0.0482$; SG 0.27 ± 0.06 % vs. SALF 0.44 ± 0.02 %, $P = 0.055$) (Fig. 3A). Further, SG mice showed significantly lower EAT and IAT/body weight ratios compared with SALF ($P = 0.0004$ and $P = 0.0001$, respectively), and PFS mice ($P = 0.001$ and $P = 0.003$, respectively). In contrast, the BAT/body weight ratio was increased in SG mice (1.3 %) compared to PFS (1 %) and SALF mice (0.9 %). Although this difference was not statistically significant for SG versus PFS mice ($P = 0.39$), the SG mice had a significantly higher BAT/body weight ratio compared SALF mice ($P = 0.049$) (Fig. 3B). As adipose tissue inflammation, mainly as a result of T cell infiltration, has been shown to play a pivotal role in mechanisms leading to insulin resistance and liver steatosis [12–14], we investigated the number of T cells responsible for the regulation of the inflammatory response in EAT. Although the $CD3^+$ T cells were equally represented in the EAT of the three groups of mice, the number of activated T

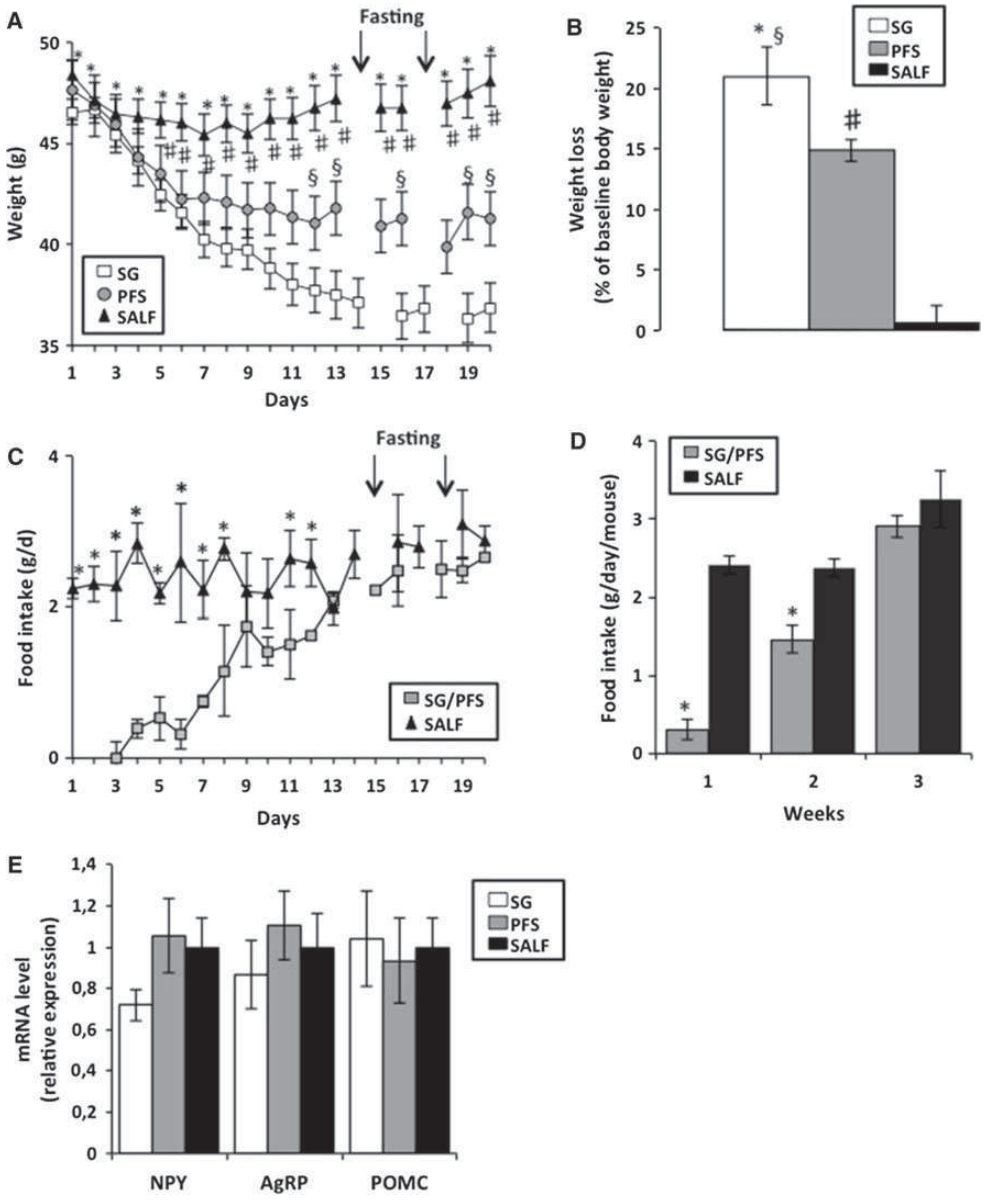

Fig. 1 Effect of sleeve gastrectomy on body weight, food intake, and the expression of melanocortin system neuropeptides. Evolution of the body weight **A**, weight loss (percentage of body weight ratio at baseline) **B**, daily food intake (mean weight (g)/mouse) **C**, and average food intake (mean weight (g)/mouse/week) **D** were evaluated in SG (10 animals), PFS (13 animals) and SALF (11 animals) mice. **E** Expression of neuropeptide Y (NPY), Agouti-related peptide (AgRP) and pro-opiomelanocortin (POMC), in the hypothalamus arcuate nucleus in SG (10 mice), PFS (13 mice) and SALF mice (11 mice) at 23 days after the surgery. The gene expression of the peptide was normalized to the mRNA levels of GAPDH. Results are expressed relative to the expression level of the SALF group and expressed as mean ± SEM. *PFS* pair-fed sham-operated, *SALF* sham-operated ad libitum fed, *SG* sleeve gastrectomy. Mann–Whitney *U* test $^{*}P < 0.05$ between SG and SALF mice, $^{\#}P < 0.05$ between PFS and SALF mice, $^{\S}P < 0.05$ between SG and PFS

cells, as evaluated by the CD44/FOXP3 ratio, was decreased, and the number of anti-inflammatory regulatory T (Treg) cells, as evaluated by the intracytoplasmic expression of FOXP3, was increased in the EAT of SG mice compared to PFS and SALF mice (Fig. 3C). These data indicate that SG mice not only had less EAT

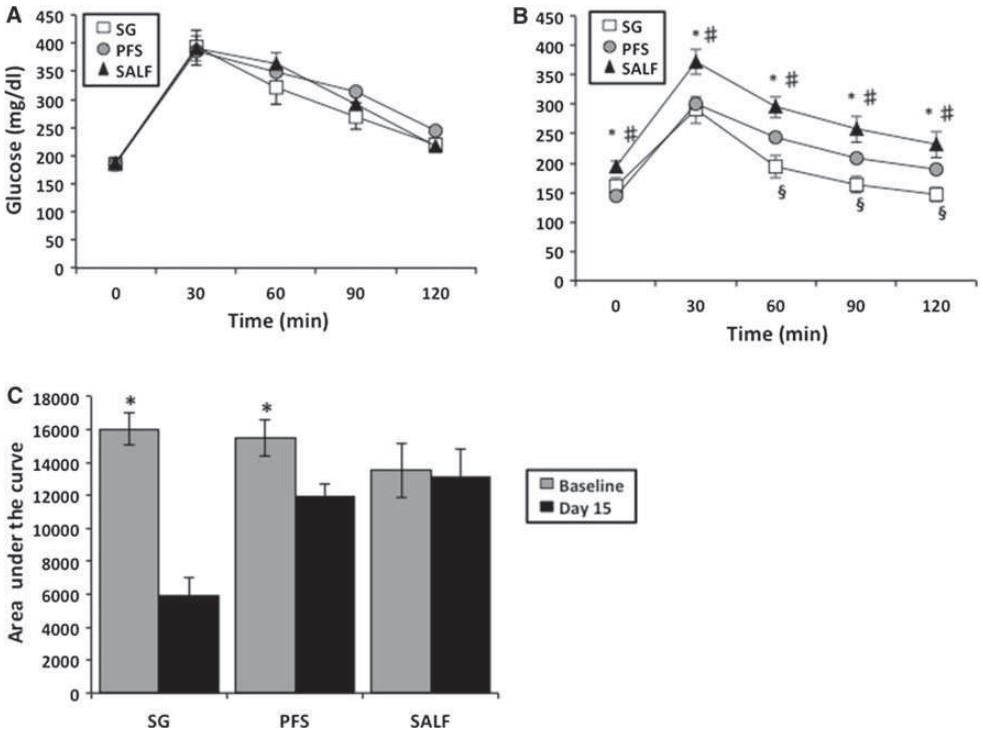

Fig. 2 Effects of sleeve gastrectomy on glucose tolerance. Intraperitoneal glucose tolerance test (IGTT) at baseline **A** and on day 15 after surgery **B.** Mean area under the curve (AUC) of the glucose tolerance test **C** in SG (10 animals), PFS (13 animals), and SALF (11 animals) mice. *PFS* pair-fed sham-operated, *SALF* sham-operated ad libitum fed, *SG* sleeve gastrectomy. Data are shown as mean ± SEM. Mann–Whitney *U* test $^{*}P < 0.05$ between SG and SALF mice. $^{\#}P < 0.05$ between PFS and SALF mice. $^{\S}P < 0.05$ between SG and PFS

quantitatively, but also that the T-cell balance was in favor of a decreased inflammatory response.

Liver steatosis and serum transaminases

Because fat tissue plays an important role in the genesis of insulin resistance and liver complications, we then evaluated the effect of SG on liver complications. As an indicator of liver damage, the variation in the transaminases level versus baseline values were first evaluated. The ALT and AST levels, as percentage of baseline values, decreased more significantly in SG mice compared to SALF mice ($P = 0.002$ and $P = 0.0015$, respectively) and PFS mice ($P = 0.046$ and $P = 0.019$, respectively) (Fig. 4A, B). Further, SG mice showed significantly less steatosis compared with SALF (6.7 % ± 1.7 vs. 30.9 % ± 5.2, $P = 0.001$) and PFS mice (6.7 % ± 1.68 vs. 16.6 % ± 3.9, $P = 0.04$) (Fig. 4C–F). Although reduced caloric intake was already associated with less liver disease (PFS mice), SG was related to normalization of the transaminases levels and a strong improvement in hepatic steatosis.

Discussion

We demonstrated that the additional loss of weight, the improvement in glucose tolerance, and the decrease in liver steatosis observed after SG in HFD-induced obese mouse cannot be explained exclusively by reduced caloric intake.

We found a loss of weight in the SG mice that remained significant throughout the duration of the study even though the mice were kept on a HFD after surgery. Interestingly, SG mice showed a significant lower food intake for the first 2 weeks after surgery, which became comparable to SALF on the third week, indicating that SG mice spontaneously increased their daily intake of food. Although this might be explained by the spontaneous dilation of the stomach, as observed sometime in humans, we did not find any significant dilation of the gastric tube at the time of the animal's death (data not shown).

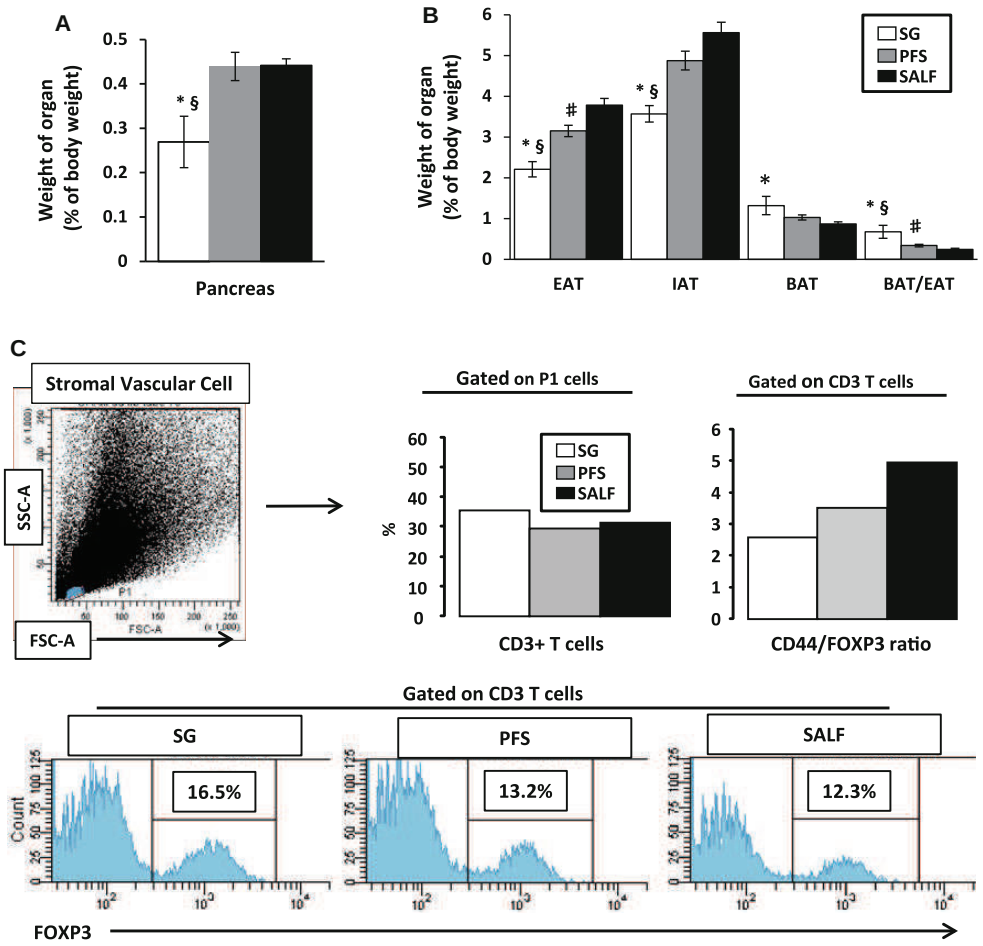

Fig. 3 Effects of sleeve gastrectomy on body fat composition and characterization of $CD3^+$ T cells in epididymal adipose tissue. Ratio of the weight of the pancreas to body weight **A**. Ratio of the weight of the epididymal adipose tissue (EAT), inguinal adipose tissue (IAT), and brown adipose tissue (BAT) to the body weight **B**. Weights were evaluated at the time of death of SG (10 animals), PFS (13 animals), and SALF (11 animals) mice. **C** Characterization of the $CD3^+$ T cells in adipose tissue from SG, PFS, and SALF mice. Epididymal fat pads were isolated, and the stromal vascular fraction (SVF) was stained for CD3, CD44, or FOXP3. Cells were gated on the nongranular and small-size populations (P1) and then on the $CD3^+$ population. (*Top*) For the FOXP3 marker, cells were stained with an anti-FOXP3 antibody. (*Bottom*) *SSC-A* side-scatter area, *SVF* stromal vascular fraction. *PFS* pair-fed sham-operated, *SALF* sham-operated ad libitum fed, *SG* sleeve gastrectomy. Data are shown as mean ± SEM. Mann–Whitney *U* test. $^*P < 0.05$ between SG and SALF mice. $^{\#}P < 0.05$ between PFS and SALF mice. $^{\S}P < 0.05$ between SG and PFS

Nevertheless, the initial decrease in dietary intake could be explained by the restrictive effects of postoperative edema and tissue inflammation at the gastric suture line in the SG group, which usually decreases within a few days of surgery. Stefater et al. also found temporary anorexia in the obese rat after SG followed by a progressive increase in food intake, which reached sham-treated ad libitum–fed controls by day 16 while weight loss was persistent. The authors reported that SG rats adapt their meal pattern, eating smaller but more frequent meals [15]. In HFD-fed obese mice, Yin et al. found a significant loss of weight after SG, which was maintained at 8 weeks in spite of the persistence of the HFD after surgery. Unfortunately, the food intake and the sham-treated pair-fed group were not evaluated [9]. Indeed, our data indicate that reduced caloric intake accounted for a loss of weight of 15 % of the baseline body weight (PFS), while the SG mice showed an additional loss of 6 % of body weight, which could not be explained by the reduced intake of food. Further, the regulation of the food intake by the central nervous system

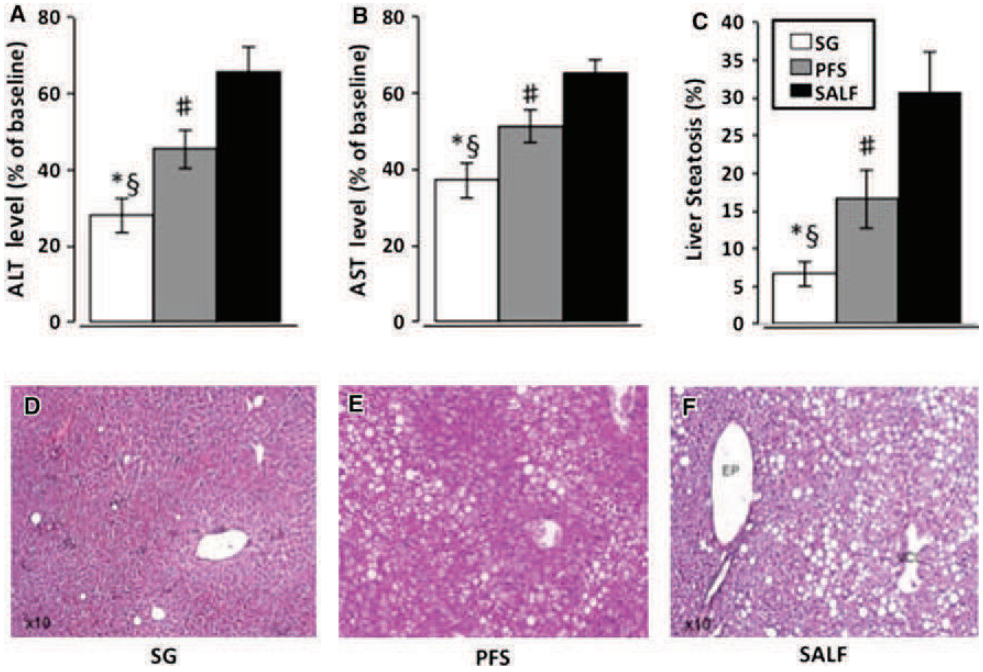

Fig. 4 Effect of sleeve gastrectomy on the serum transaminases level and on hepatic steatosis. Serum levels (percentage of baseline) of alanine aminotransferase (ALT) **A**, aspartate aminotransferase (AST) **B** (day 20 after surgery), and liver steatosis **C** (day 23 after surgery) were evaluated in SG (10 animals), PFS (13 animals), and SALF (11 animals) mice. Typical pictures of hematoxylin and eosin–stained liver sections from SG **D**, PFS **E**, and SALF **F** mice are shown. *PFS* pair-fed sham-operated, *SALF* sham-operated ad libitum fed, *SG* sleeve gastrectomy. **A**–**C** Data are shown as mean ± SEM. Mann–Whitney *U* test. $^{*}P < 0.05$ between SG and SALF mice. $^{\#}P < 0.05$ between PFS and SALF mice. $^{\S}P < 0.05$ between SG and PFS

was not modified 3 weeks after surgery. Some neurons in the hypothalamic arcuate nucleus (ARC) coexpress NPY and AgRP, which stimulate food intake and weight gain, while another population of neurons express pro-opiomelanocortin (POMC), which promotes weight loss [16]. Evaluation of the gene expression of NPY, AgRP and POMC in our mice displayed no significant difference between SG and control mice (PFS and SALF). This nonsignificant difference in levels may not have influenced food intake, but the trend was for lower levels of NPY and AgRP in the SG group, which may have an effect on energy expenditure [17, 18]. Although we measured ARC peptide expression on postoperative day 23, when the food intake was similar between SG and control mice, Stefater et al. found the same results in obese rats undergoing SG, not only on postoperative day 122, but also immediately after surgery (days 9 and 35), when animals were still experiencing a transient anorexic state [15]. Thus, these results could indicate that ARC peptides are not responsible for the maintenance of weight loss after SG.

Interestingly, Bueter et al. [19] provided evidence that gastric bypass was associated with increased energy expenditure in obese rats. As gastric bypass increases postprandial plasma levels of PYY and GLP1 [20], the authors speculated that this might be responsible for the increased energy expenditure through interference with central neuroendocrine signaling in the hypothalamic arcuate nucleus [19]. Because the difference in body weight in our study remained significant in spite of comparable food intake, we investigated the development of BAT as a potential mechanism responsible for the persistence of weight loss. Although white adipose tissue is the main storage site of excess energy, primarily in the form of triglycerides, BAT can disperse energy as heat [21]. Interestingly, we found that SG mice had a significant decrease in white adipose tissue, including IAT and EAT, but that the BAT/body weight ratio tended to increase, although this difference was not statistically significant between SG versus PFS mice. However, the BAT/EAT ratio progressively increased with PFS and then SG compared to SALF mice (SALF: 0.246 ± 0.025 vs. SPF: 0.339 ± 0.033 vs. SG: 0.676 ± 0.157; SG vs. PFS, $P = 0.025$; SG vs. SALF, $P = 0.0018$; PFS vs. SALF, $P = 0.025$). These data suggest that a modification in the specific fat depot (brown vs.

white adipose tissue) may participate in the persistence of weight loss in SG mice in spite of the increased food intake.

Visceral white adipose tissue is responsible for the low-grade inflammatory state of obese subjects through the secretion of soluble mediators of inflammation [22]. There is also evidence that soluble mediators of inflammation are implicated in mechanisms leading to insulin resistance by interfering with the disruption of insulin signaling through serine phosphorylation of the insulin receptor substrate [23–25]. Furthermore, it has been shown that T cells play a pivotal role in regulating the inflammatory response in the adipose tissue [12–14, 26]. We thus investigated the number of T cells in the EAT, which is the equivalent of human visceral adipose tissue in rodents. Although the absolute number of $CD3^+$ T cells was not different for SG and control mice, the former had an increased number of $FOXP3^+$ T cells, which are implicated in anti-inflammatory signals blocking adipose tissue inflammation, and a decreased number of pro-inflammatory activated T cells, as evaluated by the CD44/FOXP3 ratio. SG thus was associated with a T-cell balance in EAT that was indicative of a decrease in the inflammatory response. This observation was in accordance with our previous reports on the decrease in adipose tissue and systemic inflammation associated with gastric bypass in patients [11, 27–29]. Thus, the reduced amount of EAT coupled with a reduced inflammatory response, and the potential concomitant reduction in the levels of circulating cytokines observed in SG mice are consistent with a casual role in SG-induced improvement of glucose tolerance.

Insulin resistance is the common denominator of the metabolic disturbances associated with obesity, which include the accumulation of triglycerides in the liver that leads to hepatic steatosis. Indeed, the improvement in glucose tolerance we observed in SG mice compared to control mice was associated with a decrease in liver steatosis in SG mice, which was superior to that observed in the control groups (PFS mice). As expected, the decrease in liver steatosis was associated with a significant decrease in the level of serum transaminases.

We also investigated the role of ghrelin, the potent orexigenic hormone secreted primarily by the gastric mucosa, which has been considered as a main actor responsible for the effects of SG, not only on the balance in energy expenditure but also on the metabolic disturbances linked to obesity [30]. In our study, SG mice showed reduced circulation levels of acyl ghrelin, the active form of ghrelin, compared with control mice. Chambers et al. [31] recently demonstrated in ghrelin-deficient mice that the effect of SG on weight loss, food intake, and glucose tolerance was independent of ghrelin signaling. However, developmental compensations in ghrelin-deficient mice may lead to underestimate the role of ghrelin reduction to the effects of SG. Indeed, Longo et al. [30] showed that chronic pharmacological blockade of the ghrelin receptor was associated with a striking improvement in hepatic insulin sensitivity, insulin secretion, decreased hepatic steatosis, and better liver function. The reduced circulating levels of ghrelin we found in SG mice may thus influence the mechanisms responsible for the dramatic reduction in liver steatosis that we observed in SG mice compared with control mice.

There is evidence in the literature of the inhibitory effect of fatty acids on insulin secretion in vitro and in vivo [32–34] and the association between pancreatic fat content and type two diabetes [35], with a sharp increase in both the total pancreatic fat and islet triacylglycerol content before the onset of spontaneous diabetes in rodents [36, 37]. Furthermore, Pinnick et al. [38] demonstrated that mice fed a HFD for 15 weeks had a higher triacyglycerol content compared to control mice fed a normal diet. As mice in the present study were fed a HFD for 32 weeks before surgery, we investigated the effect of SG on the pancreas/body weight ratio and found that SG mice showed a ratio significantly lower in spite of a greater weight loss compared with both control groups. We speculate that a possible decrease in pancreatic fat after SG may contribute to the strong improvement in glucose tolerance observed in SG mice that could not be explained exclusively by the reduced caloric intake in our study.

We acknowledge that there are some limitations of the present study. We did not investigate the energy expenditure (body temperature, basal metabolic rate), locomotor activity, gut function (lipid absorption, gut permeability, endotoxinemia), and gut hormones (GLP-1, PYY, CCK), which have important metabolic effects after SG and might account for the difference in weight loss between SG and PFS mice.

Others have previously demonstrated the effect of SG and reduced caloric intake on glucose, lipid metabolism, and blood pressure in rat model [39, 40]. We have also evaluated the effect of the SG in a HFD mice model. Indeed, mice were fed the same HFD before but also after surgery, leading to the evaluation the role of SG even without modification of the diet. We report a modification in the specific fat depot (brown vs. white adipose tissue) in response to SG that may participate in the persistence of weight loss in SG mice in spite of the increased food intake. Further, the beneficial effect of SG correlated with less activated T cells and by more anti-inflammatory regulatory T cells in epididymal adipose tissue. Altogether, these responses mediated by SG prevent the ectopic fat accumulation in both liver and pancreas even in HFD. This effect cannot be explained exclusively by reduced caloric intake. In our study, SG proved more effective than simple reduced caloric intake in reducing body weight, in restoring

glucose tolerance, and in decreasing liver steatosis in HFD-induced obese mice. Modification of adipose tissue development (brown vs. white adipose tissue) and ectopic fat (pancreatic steatosis) could also be involved. Thus, SG is not a purely restrictive procedure but has several metabolic effects such as decreased ghrelin levels and increased insulin, PYY, and GLP-1 levels, unlike other purely restrictive procedures as such gastric banding and vertical banded gastroplasty [7].

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Assessment of Different Bariatric Surgeries in the Treatment of Obesity and Insulin Resistance in Mice

To the Editor:

In the July 2011 issue of ***Annals of Surgery***, Yin et al[1] reported the results of different bariatric surgical procedures in the treatment of obesity and insulin resistance in mice. The authors found that the sleeve gastrectomy and a modified Roux-en-Y gastric bypass (mRYGBP), in which the whole stomach is bypassed, represent reliable restrictive and gastrointestinal bypass bariatric models. With respect to the efficacy of these 2 procedures against excess weight, liver steatosis, altered glucose tolerance, and pancreatic islet viability, they found that the mRYGBP provides better and more durable results than sleeve gastrectomy. Indeed, animals undergoing sleeve gastrectomy progressively regained the lost weight between 4 and 8 weeks.

We congratulate the authors for their remarkable work; however, we feel, at the same time, that their report raises a few issues that need further discussion. First, in the case of the sleeve gastrectomy, the fact that only 90% of the forestomach is removed conflicts with the statement that the whole gastric fundus is removed. In our experience, 10% of the residual forestomach inevitably dilates between 4 and 8 weeks after surgery, leading to weight gain as observed by the authors (Fig. 3A). We encountered the same problem during the preparation of a sleeve gastrectomy model in the mouse. When the forestomach was not carefully and completely resected, animals showed progressive weight gain that was paralleled by an increase in the daily quantity of ingested food. At necropsy between 4 and 8 weeks after surgery, we found a dilatation of the remnant forestomach. This prompted a modification of the surgical technique that includes the complete and careful removal of the forestomach along with the resection of the glandular stomach. The authors state that they remove 70% to 80% of the stomach at the time of sleeve gastrectomy and provide interesting imaging data of the gastrointestinal tract showing the reduction of the stomach volume at 7 to 10 days after surgery. However, no collective data are provided on the average reduction of the stomach as evaluated on computed tomographic scan in the 14 mice undergoing sleeve gastrectomy. Imaging data after weight regain, that is, between 4 and 8 weeks, would provide useful information on the mechanisms underlying weight gain after sleeve gastrectomy, such as the dilatation of the remnant stomach that is frequently seen in the humans after this procedure.

The results of the bariatric surgery groups of animals in terms of weight loss, glucose tolerance, body composition, liver steatosis, and pancreatic islet viability were compared with control animals (lean, diet-induced obese, and a pool of sham animals) that were fed ad libitum after surgery. Although the authors conclude that bariatric surgery improves glucose tolerance and regulates pancreatic islet viability in the mouse, the experiments they presented do not allow such a conclusion as they lack a control group of pair-fed, sham-operated animals. The latter consist of a group of animals that are given an amount of food that corresponds exactly to the quantity of food eaten by animals in the bariatric surgery groups. As a consequence, the authors cannot conclude that the changes they observed are due to the effects of bariatric surgery other than food restriction and loss of body weight. In other words, the lack of pair-fed, sham-operated control group limits the conclusion that may be driven by these experiments. Sleeve gastrectomy improves glucose tolerance at 4 weeks, but no difference is observed with sham-operated animals at 8 weeks. If this difference was only due to the effect of food restriction and loss of body weight, a pair-fed, sham-operated control group of animals would behave as the animals of the sleeve gastrectomy group, that is, improving the glucose tolerance at 4 weeks after surgery and recurring glucose intolerance at 8 weeks. Furthermore, animals undergoing the mRYGBP show a stronger improvement of the glucose tolerance at 4 weeks that persists at 8 weeks. Again, it is not clear whether this phenomenon is due to the fact that the mRYGBP implies a severe food restriction and a more important loss of body weight that is not reversible as the stomach is completely bypassed or whether factors other than hypophagia and weight loss alone play a determinant role as already shown in humans and rodents.[2,3] Indeed, the reduction of fat mass has been considered for a long time as the main mechanism responsible for the positive effect of bariatric surgery on type II diabetes mellitus.[4] However, the fact that RYGBP[5] and sleeve gastrectomy[6] are followed by rapid and significant control of type II diabetes mellitus, sometime within days after surgery, has raised the hypothesis that mechanisms other than the loss of body weight are involved in the control of the metabolism of glucose. In an elegant study in humans, a group of diabetic patients undergoing sleeve gastrectomy were compared with a pair-fed group of diabetic patients undergoing a laparoscopic cholecystectomy. Not surprisingly, patients in the sleeve gastrectomy group showed an improved tolerance to glucose immediately after surgery that was not observed in the pair-fed, operated control group of patients undergoing a simple cholecystectomy.[7] This study, although interesting, has several limitations that cannot be overcome in humans.

We found in a mouse model of sleeve gastrectomy that when adequate pair-fed, [AQ3] sham-operated controls are provided, pair-fed, sham-operated animals lose more weight than sham animals fed ad libitum, but not as much as animals undergoing sleeve gastrectomy, indicating that other mechanisms than pure food restriction and loss of body weight are involved in the loss of weight after bariatric surgery.

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Deuxième volet

L'obésité s'associe à des complications hépatiques graves telles que les stéatohépatites métaboliques. Celles-ci sont regroupées sous le terme NAFLD (Non-Alcoholic Fatty Liver Disease) comprenant des lésions histologiques qui vont de la simple stéatose à la stéatohépatite (NASH), la fibrose, la cirrhose et au carcinome hépatocellulaire. La NASH est devenue la troisième indication de transplantation hépatique aux Etats-Unis (Agopian et al., 2012) et expose à un risque accru de développer un carcinome hépatocellulaire (Baffy et al., 2012). Plusieurs études ont montré l'efficacité de la chirurgie bariatrique sur la perte de poids et sur la rémission des comorbidités associées à l'obésité. Cependant, peu d'études ont évalué les effets de la chirurgie de l'obésité sur la NAFLD. Le diagnostic de NAFLD est histologique. Cela implique donc la réalisation d'une deuxième biopsie à distance de la chirurgie bariatrique pour prouver l'évolution des lésions hépatiques. La biopsie est un geste invasif qui peut être responsable d'une morbidité spécifique (Terjung et al., 2003). La nécessité d'une deuxième biopsie explique la rareté de ce type d'études en littérature. Quand on analyse les séries publiées, on rencontre plusieurs problèmes liés à l'hétérogénéité des données. Différents types d'interventions sont pris en compte, beaucoup d'études ont analysé les effets sur la stéatose, mais peu d'études ont étudié l'inflammation et la fibrose. Un autre problème rencontré est l'intervalle entre l'intervention bariatrique et la seconde biopsie qui est en général inférieur à 24 mois. Parmi les séries de la littérature, les données les plus consistantes proviennent de l'équipe lilloise qui a publié des données issues de la plus large cohorte de patients obèses morbides opérés d'une chirurgie bariatrique et qui ont eu une deuxième biopsie hépatique (Mathurin et al., 2006). Dans une première étude sur une cohorte de 185 patients, ils rapportent les effets de l'anneau gastrique (AGB) et

du bypass bilio-intestinal sur la stéatose à un an. Dans une deuxième étude ils rapportent les effets de l'AGB, du bypass bilio-intestinal et du Gastric Bypass en Roux-en-Y (RYGBP) à 5 ans. Ils confirment l'efficacité de la chirurgie sur la stéatose et montrent une amélioration significative de la fibrose à 5 ans chez 211 patients. Dans cette étude 18 patients avaient une NASH définie par un NAS score ≥ 5. Dans ce sous-groupe de patients il y a une amélioration significative de la stéatose, de la souffrance hépatocytaire (ballonisation) et du score NAS. Par contre, ils ne montrent pas d'amélioration de l'inflammation hépatique (Mathurin et al., 2009a). Dans une étude longitudinale comparant le RYGBP et l'AGB la même équipe a récemment montré la supériorité du RYGBP sur la rémission de la NAFLD à 3 ans et 5 ans (Caiazzo et al., 2014). Cette étude est la seule en littérature qui compare deux opérations bariatriques par rapport à leur efficacité sur la NAFLD. En outre, cette étude prouve que la restriction alimentaire et la perte de poids jouent un rôle essentiel dans l'évolution de la NAFLD compte tenu des résultats obtenus avec l'AGB qui est une opération purement restrictive. Les auteurs concluent à une supériorité du RYGBP due à la perte de poids plus importante mais aussi à l'existence de mécanismes autres que la restriction pure - le seul mécanisme d'action de l'AGB. Ces résultats concordent avec les résultats que nous avons trouvé dans le modèle animal de SG pour lequel nous disposions d'un groupe contrôle pour la restriction alimentaire (Sham Pair Fed). Mais dans cet article, il n'y a que 12 patients avec un diagnostic de NASH (NAS score ≥ 5).

Les études publiées sur les effets de la chirurgie bariatrique sur la NASH comportent peu de patients (Tableau 3).

	Année	Nb de patients	RYGBP	NASH	Stéatose	Inflammation	Ballonisation	NAS Score	Fibrose	Suivi (mois)
Silverman	1995	91	91	NR	NR	NR	NR	NR	NR	18,4
Clark	2005	16	16	NR	NR	NR	NR	NR	NR	10
Mottin	2005	93	93	5	oui	NR	NR	NR	NR	12
Mattar	2005	70	NR	NR	oui	oui	non	oui	oui	15
Barker	2006	19	19	19	oui	oui	oui	oui	oui	21,4
Csendes	2006	16	16	5	oui	oui	oui	oui	non	17,5
de Almeida	2006	16	16	16	oui	non	oui	oui	non	23,5
Liu	2007	39	39	23	oui	oui	oui	oui	oui	18
Furuya	2007	18	18	12	oui	oui	oui	oui	oui	24
*Mathurin**	2009	381	80	NA	oui	oui	oui	oui	oui	60
Weiner	2010	116	68	NA	oui	oui	oui	oui	non	18,6
Moretto	2012	78	78	45	NR	NR	NR	NR	oui	NA
Tai	2012	21	21	4	oui	oui	oui	oui	oui	12
*Caiazzo **	2014	413	167	12	oui	oui	oui	oui	oui	60
Total		**1006**	**642**	**141**						**20,9**

Tableau 3. Les séries de littérature rapportant des résultats du RYGBP sur la NALFD.
** Les 2 études sont issues de la même série, seule la dernière est prise en compte dans les calculs d'effectifs. NR : non renseigné*

Seulement une partie de ces patients a eu un RYGBP et la deuxième biopsie a été réalisée à un intervalle de temps variable. Entre 1995 et 2014, un total de 642 patients obèses morbides opérés d'un RYGBP ont eu une seconde biopsie afin d'évaluer l'évolution des lésions hépatiques. Le suivi a varié entre 10,2 à 60 mois. Cependant une seule équipe (deux séries) a rapporté les résultats à 5 ans sur 12 malades dont certains ont un AGB (Mathurin et al., 2009b) (Caiazzo et al., 2014). Aucune aggravation de la stéatose ou de l'inflammation n'a été documentée. Moretto *et al.* ont étudié l'évolution de la fibrose chez ces patients. Sur 78 patients, dont 45 patients de NASH, 35 patients (44,9%) n'avaient pas de fibrose, 31 (39,7%) présentaient une fibrose péri-sinusoïdale et/ou lobulaire, 4 (5,1%) une fibrose portale et 7 (10,3%) une fibrose lobulaire et portale. La présence d'une fibrose était significativement associée avec le diabète de type 2 et la dyslipidémie. Lors de la seconde biopsie, la fibrose a été retrouvée chez 24 (20,8%) patients, dont 5 (6,4%) qui n'avaient pas de fibrose initialement (Moretto et al., 2012).

Compte tenu de l'hétérogénéité de ces données, nous avons voulu étudier une population homogène de patients obèses morbides opérés d'un RYGBP avec un diagnostic histologique de NASH au moment de la chirurgie. Les patients sont issus d'une base prospective longitudinale de patients obèses morbides opérés d'une chirurgie bariatrique au CHU de Nice depuis 2003. Les patients qui acceptent de rentrer dans cette cohorte ont un bilan métabolique, et une prise de sang pour la constitution d'une sérothèque avant la chirurgie. Une biopsie hépatique est réalisée durant la chirurgie qui est en partie analysée et en partie stockée dans une tissuthèque. Le bilan métabolique est réalisé à 6 mois et à 1 an de manière systématique et des échantillons de sérum sont stockés dans la sérothèque.

A partir de cette cohorte, nous avons sélectionné les patients qui présentaient un NAS score ≥ 5, un suivi minimum de 3 ans, un bilan métabolique préopératoire complet ainsi qu' une biopsie hépatique au moment du RYGBP exploitable. En plus, ils devaient avoir accepté la deuxième biopsie hépatique percutanée. Il y a 10 patients qui ont eu une deuxième biopsie et font l'objet de cette étude prospective, longitudinale visant à étudier l'évolution des lésions histologiques de la NASH long terme après RYGBP. Les résultats de cette étude concordent avec ceux de la littérature sur l'évolution favorable à long terme de la stéatose qui est améliorée chez tous les patients et résolue chez 50 % d'entre eux. Nous avons aussi montré que l'inflammation hépatique et la souffrance hépatocytaire sont résolues chez respectivement 100% et 90% des patients. En conséquence, le score NAS est amélioré chez tous les patients. La rémission des lésions histologiques du foie corrèle avec la rémission du syndrome métabolique, de l'inflammation systémique et la stabilité de la perte pondérale. Ces résultats sont d'autant plus intéressants compte tenu de la durée médiane du suivi de 57 mois, de la caractérisation exhaustive et l'homogénéité de la cohorte.

Le M30 est le fragment soluble du filament intermédiaire de la Kératine 18 (K18) contenant le néo-épitope M30 (K18Asp396-NE) qui est libéré après le clivage par les caspases et qui reflète la mort cellulaire par apoptose. Dans une étude préliminaire, nous avons montré que le «M30» est associé à la NASH et qu'il est absent dans le sérum des patients atteints d'une stéatose, même grave (figure 3D de l'article suivant). Chez les patients avec une NASH histologiquement prouvée au moment de la chirurgie bariatrique, le taux sérique du M30 était normalisé à 6 mois et restait normal à un an. Nous avons donc émis l'hypothèse que le taux sérique du marqueur sérique du M30 diminue de manière consensuelle avec la rémission histologique de la NASH. Nous avons mesuré le M30 chez les 10 patients au moment de la deuxième biopsie hépatique. En effet, la rémission histologique de la NASH après le RYGBP corrèle avec la diminution du taux sérique du M30 qui atteint les valeurs retrouvées chez les patients sans NASH. Bien que cette hypothèse doive être validée dans une autre cohorte plus large, le M30 pourrait devenir un marqueur sérique non-invasif permettant d'évaluer la rémission des lésions histologiques de NASH chez l'obèse après la chirurgie bariatrique.

Roux-en Y gastric bypass results in long-term remission of hepatic steatosis, inflammation and hepatocyte apoptosis in non-alcoholic steatohepatitis patients

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Short title: RYGB effects on NASH.

Keywords: human, obese, RYGB surgery, hepatic injury, steatosis, non-alcoholic steatohepatitis; NASH, NAFLD

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ABSTRACT

Objective: To investigate the long-term impact of laparoscopic Roux-en-Y gastric bypass (LRYGB) surgery on liver complications in morbidly obese patients with non-alcoholic steatohepatitis (NASH).

Design: Ten morbidly obese patients (median BMI: 41.9 [38.8; 45.0] kg/m^2) with biopsy-proven severe hepatic steatosis and NASH (nine with NAS 5, and one with NAS 6) were followed after LRYGB and underwent a second liver biopsy. The median interval between the LRYGB and second liver biopsy was 57 [44; 79] months. Clinical and biological data, including serum caspase-generated keratin-18 fragment (K18 fragment), were obtained at baseline, 6 months, 12 months, and ≥40 months after LRYGB.

Results: LRYGB was associated with significant weight loss (median BMI loss –13.3 [–15.9; –9.3] kg/m^2), improved hepatic steatosis in all patients (50% with total resolution), and resolution of hepatic inflammation and hepatocyte ballooning in 100% and 90% of cases, respectively. Accordingly, NAS improved in all patients (five with NAS 0). Alanine aminotransferase levels dropped to normal values after a median follow-up of 57 months. Hepatocyte apoptosis, as evaluated by serum K18 fragment improved within the first year and these changes persisted for at least 57 months. Hepatic fibrosis resolved in 90% of cases but was slightly increased in one patient.

Conclusions. LRYGB in morbidly obese patients with NASH is associated with a long-term beneficial impact on hepatic steatosis, inflammation, injury and, possibly, fibrosis.

Abstract: 224 words

INTRODUCTION

The prevalence of obesity has increased dramatically in recent years and nowadays represents a major health burden [1]. With the epidemic of obesity, comorbidities associated with this condition have also increased [2]. Indeed, non-alcoholic fatty liver disease (NAFLD) has become the most common liver disease in Western countries [3]. NAFLD includes a spectrum of liver anomalies, from simple steatosis to non-alcoholic steatohepatitis (NASH), and is characterized by the presence of liver injury (hepatocytes ballooning and apoptosis), inflammation and, finally, liver cirrhosis, eventually leading to hepatocellular carcinoma [4, 5]. Recent data indicate that NASH is the third most common indication for liver transplantation in the United States [6].

In parallel with the epidemic of obesity, bariatric surgery has emerged as the only therapeutic treatment that results in long-term weight loss and improvement or resolution of most obesity-related comorbidities [7, 8]. However, evidence of the long-term efficacy of bariatric surgery against NASH is lacking. Most series in the literature report heterogeneous data derived from series that have included a variety of bariatric procedures with the follow-up period limited to 2 years [9][10][11][12][13][14][15][16][17][18][19][20]. Thus, we decided to study the long-term effects of bariatric surgery on liver complications caused by obesity. With this aim, we designed a study with sequential liver biopsies in a well-characterized cohort of morbidly obese patients with NASH and undergoing laparoscopic Roux-en-Y gastric bypass (LRYGB) surgery.

EXPERIMENTAL PROCEDURES

Study design

Patients included in this study were identified from an ongoing prospective study on morbidly obese patients who met the NIH criteria for bariatric surgery [21] and undergoing bariatric surgery at the Department of Digestive Surgery and Liver Transplantation of the University of Nice (France). All patients had a preoperative work-up (repeated at 6 and 12 months after surgery) and underwent a wedge-liver biopsy at the time of surgery. A second liver biopsy and a concomitant diagnostic work-up was offered to patients who underwent a LRYGB, and who initially presented with criteria for NASH (on a liver biopsy) and completed a minimum follow-up period of 36 months after surgery. In addition, data from blood samples obtained from five morbidly obese patients, included in the same prospective ongoing study and who had no sign of NAFLD in the liver histology (aged 37 ± 10 years; BMI 44 ± 3 kg/m^2), from seven patients with biopsy-proven severe hepatic steatosis (aged 34 ± 8 years; BMI 46 ± 8 kg/m^2), and from seven patients with biopsy-proven NASH (aged 40 ± 8 years; BMI 41 ± 3 kg/m^2) were also used in this study (**Figure 1**).

Human studies

Ten morbidly obese patients were included in this study. Exclusion criteria were the presence of a hepatitis B or hepatitis C infection, excessive alcohol consumption (>20 g/d) or any other cause of chronic liver disease as previously reported [19-20-21]. The patients' characteristics are described in Table 1. Before surgery and during the follow-up (6 months, 12 months, and the last follow-up visit before the second liver biopsy), fasting blood samples were obtained and analysed for alanine

aminotransferase (ALT), glucose and insulin, triglycerides, high-density lipoprotein (HDL)-cholesterol, C-reactive protein and caspase-generated keratin (K18 fragment). Metabolic syndrome was diagnosed according to the modified International Diabetes Federation (IDF), to include three or more of the following criteria: (i) central obesity defined by an increased waist circumference (≥80 cm in women and ≥94 cm in men), (ii) triglycerides ≥1.7 mmol/L or treatment for hyper-triglyceridemia; (iii) HDL-cholesterol <1.29 mmol/L in women and <1.03 mmol/L in men; (iv) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or treatment for hypertension, and (v) fasting plasma glucose ≥5.6 mmol/L or previously diagnosed type-2 diabetes mellitus [25]. Type-2 diabetes was defined by two measurements of elevated fasting plasma glucose ≥7 mmol/L. Insulin resistance was evaluated using the homeostatic model assessment (HOMA-IR) index [26].

Ten patients with biopsy-proven NASH had liver biopsies repeated at a median follow-up of 57 [44; 79] months after surgery. The first liver biopsy was a 15-mm-long wedge biopsy obtained during surgery, with no ischemic preconditioning. The second was a needle-biopsy of the liver, obtained by the transparietal approach. Biopsies were processed routinely and stained with hematoxylin–eosin–saffron and sirius red. Liver biopsies were reviewed by two liver pathologists (SP and MC-SP) who were blinded to the clinical and biological characteristics of the patients. Histopathological analyses were performed according to the scoring system of Kleiner *et al.* [27]. Four histopathological features were semi-quantitatively evaluated: grade of steatosis (0, <5%; 1, 5–33.3%; 2, >33.3–66.6%; 3, >66.6%), lobular inflammation (0: no inflammatory foci; 1: <2 inflammatory foci per 200x field; 2: 2–4 inflammatory foci per 200x field; 3: >4 inflammatory foci per 200x field), hepatocellular ballooning (0, none; 1, few balloon cells; 2, many cells/prominent ballooning), and stage of fibrosis (from

0=none, to 4=cirrhosis). The NAFLD score (NAS) is defined as the unweighted sum of scores for steatosis (0 –3), lobular inflammation (0 –3), and ballooning (0 –2), thus ranging from 0 to 8 [27].

All subjects gave their informed written consent to participate in this study in accordance with French legislation regarding Ethics and Human Research (Huriet-Serusclat law). The “Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Nice” approved the study (07/04:2003, N° 03.017).

Circulating levels of transaminases and K18 fragment. Determination of plasma alanine aminotransferase (ALT) was performed using an *in vitro* test with pyridoxal phosphate activation on a Roche/Hitachi cobas c system (ALTPM, cobas, Meylan, France). Keratin 18 (K18) is cleaved by the caspases during apoptosis, generating soluble protein fragments. The M30 Apoptosense® ELISA assay specifically measures apoptosis (the caspase-generated K18 fragment, K18-Asp396). All samples were analysed as described in the manufacturer’s instructions and in duplicate. The within assay (WA% CV) variation was <10% and between assay (BA% CV) variation was <10% for samples >100 U/L. The minimum detectable concentration was 25 U/L. Keratins are released into the circulation as protein complexes. These complexes are remarkably stable during sample collection and long-term storage. Furthermore, plasma/serum samples can be exposed to repetitive freeze–thaw cycles without loss of activity [28].

Statistical analyses

The statistical significances between the two study groups were determined using the non-parametric Mann–Whitney test and Fischer’s test. Correlations were analysed

using the Pearson's correlation test. A *P*-value of <0.05 was considered statistically significant. Quantitative variables are presented as their medians [interquartile ranges].

RESULTS

The aim of this study was to investigate the potentially beneficial effect of LRYGB on obesity-related liver complications in morbidly obese patients with histologically proven severe steatosis and NASH. Nine women and one man, with a median age of 48 [30; 59] years at the time of LRYGB, had a second liver biopsy after ≥40 months of follow-up. The median interval between the LRYGB and the second liver biopsy was 57 [44; 79] months **(Table 1).**

LRYGB improves metabolic syndrome, type-2 diabetes and systemic inflammation

We first evaluated the effects of LRYGB on weight loss, metabolic syndrome, type-2 diabetes and systemic inflammation in our NASH patients. All patients lost more than 50% of excess BMI and a median loss of –13.3 [–15.9; –9.3] kg/m^2 BMI points (**Table 1**). Insulin resistance, as evaluated by the HOMA-IR, fasting insulin and glycaemia were strongly improved after LRYGB, as shown in **Table 1**. Four patients with type-2 diabetes before surgery were in remission at the time of the follow-up. Metabolic syndrome was diagnosed in seven patients at the time of surgery and persisted in only in two patients by the end of follow-up.

Chronic low-grade inflammation, as evaluated by C-reactive protein, was also improved after a LRYGB in all patients (**Table 1**). As we and others have previously reported, at 1 year after bariatric surgery [21, 26, 27], a LRYGB has a beneficial

effect on metabolic syndrome and systemic inflammation that is maintained for the longer term.

LRYGB improves hepatic steatosis, inflammation and NAS score in all patients, and hepatic fibrosis in a large majority

We then evaluated the effect of LRYGB on obesity-related liver complications. Liver steatosis was evaluated as severe (S3, >66.6% of hepatocytes) in all patients at the time of surgery. On the second biopsy, steatosis was improved in all patients: i.e., full correction in five patients and grade 1 (<33.3 %) in five patients (**Figure 2A**). Hepatic inflammation, present in all patients at the time of surgery, was no longer present on the second biopsy in any patient (**Figure 2B**). Ballooned hepatocytes, another hallmark of NASH and a marker of liver-cell degeneration, were found in all liver biopsies at the time of surgery, but were no longer present in the second liver biopsy in nine patients (90%).

Only one patient still had ballooned hepatocytes on the liver biopsy in spite of significant weight loss, improved metabolic syndrome, insulin resistance (HOMA-IR: from 5.4–2.3), hepatic steatosis (from S3 to S1) and hepatic inflammation (**Figure 2C**). As a consequence, the NAS score, which was elevated in all patients at the time of surgery (nine patients with NAS=5, and one with NAS=6) had dropped considerably in all patients, by 2–6 full points (**Figure 2D**).

The stage of fibrosis was more heterogeneous at the time of surgery, with only one patient showing advanced fibrosis (F=3), three patients with moderate fibrosis (F=2), four patients with mild fibrosis (one with F=1B, three with F=1A) and two patients with no fibrosis (F=0). The second liver biopsy showed a significant improvement in fibrosis (F=0) in eight patients and a slight progression of liver fibrosis in one patient

(from F0–F1A) (**Figure 2E**). One patient who had no fibrosis at the time of surgery showed no signs of fibrosis on the second biopsy. LRYGB was associated with correction of hepatic steatosis and inflammation in all patients, and improvement of fibrosis in 90%.

LRYGB improves hepatic injury and hepatocyte apoptosis in all patients

NASH is characterized by fatty liver, hepatic inflammation but also the substantial death of hepatocytes [4, 28]. Hepatocyte apoptosis plays an important role in the progression and the severity of obesity-related liver complications. We thus investigated the effect of LRYGB on hepatocyte injury in the longer term. Levels of ALT in the serum reached normal-range values in all patients at the last follow-up time (ALT: 46.5 [36; 81.3] to 24.5 [22.3; 27.3] UI/L) (**Figure 3A)**.

The serum level of caspase-generated keratin 18 fragment (K18 fragment) was used to evaluate hepatocyte apoptosis. An average decrease of 30% in serum K18 fragment level was found in 90% of patients after a median follow-up of 57 [44; 79] months after the LRYGB. There was no modification for one patient who already had a low value at the time of the LRYGB (**Figure 3B)**. Interestingly, the levels of K18 fragment were significantly reduced in all NASH patients at 1 year after LRYGB, to the level that is usually found in patients without hepatic complications [32][33] (**Figure 3C).**

We also evaluated this marker in three additional groups of morbidly obese patients without any signs of NAFLD (*n*=5), severe steatosis (*n*=7) or severe steatosis associated with NASH (*n*=7): assessed from a liver biopsy at baseline and at 1 year after LRYGB. While hepatic steatosis had no effect on the level of K18 fragments, the latter was increased in patients with NASH compared with patients without NASH at

the time of surgery (**Figure 3D**). At 1 year after the LRYGB, the level of K18 fragment had strongly decreased in all NASH patients (**Figure 3E**). Altogether, these data indicate that the LRYGB had a beneficial effect on hepatocyte apoptosis by 1 year post-surgery, and that this was maintained for the median follow-up period of 57 [44; 79] months.

DISCUSSION

In this study we provide evidence that the LRYGB results in long-term improvement of hepatic steatosis (i.e., 50% with total resolution) and inflammation in all patients, and resolution of hepatocyte ballooning in 90% of patients with severe steatosis and NASH.

While there is strong evidence of the beneficial effects of the LRYGB on excess weight and resolution or reduction in type 2-diabetes (with remission in 63.5% of cases) [34], its impacts on liver complications needed to be better determined. Most studies have including paired liver biopsies and report a mean interval between a LRYGB and a second liver biopsy of 19 ± 4 (range: 12–25) months; they also mainly focus on the improvement of hepatic steatosis [9][11][12][13][14][15] [16][18] [19][20]. In contrast, the impact of LRYGB on hepatocyte ballooning and apoptosis, as well as on liver necro-inflammatory lesions and fibrosis, is still a matter of debate. Indeed, data on the long-term impact of LRYGB on NASH patients are lacking.

In this study, a second biopsy was made in morbidly obese patients with liver-biopsy-proven severe steatosis and NASH after a median interval of 57 [44; 79] months after a LRYGB. As we and others have previously reported, at one year after surgery [24,29,35], insulin resistance, metabolic syndrome and systemic inflammation had improved after a median follow-up period of 57 [44; 79] months. A beneficial impact

of LRYGB on hepatic steatosis has been observed in all patients, from total resolution (in 50% of cases) to striking improvement (S3 to S1: 50%). Because improvement of hepatic steatosis, evaluated by paired liver biopsies, has also been reported at 18 ± 5 months after LRYGB [9,11,14-16,18]-20], it may be speculated that the beneficial impact of LRYGB on insulin resistance, systemic inflammation and hepatic steatosis that occurs within the first year persists in the longer term, as shown in the present study. Accordingly, a recent meta-analysis compiled results from different bariatric procedures, including RYGB, gastric banding, sleeve gastrectomy, a duodenal switch and biliopancreatic diversion, reported the same results with improvement of hepatic steatosis in 90% of cases [10]. However, this meta-analysis was unable to evaluate the specific impact of bariatric surgery on NASH features in the longer term.

Herein, we report that NASH features, including inflammatory foci and ballooned hepatocytes, improved in, respectively, 100% and 90% of our NASH patients after a median follow-up of 57 [44; 79] months after LRYGB. As a consequence, the NAS score decreased in 100% of cases. Despite the heterogeneousness of the degree of hepatic fibrosis in our patients at the time of a LRYGB, improvement of hepatic fibrosis occurred in 90% of cases. One patient showed a slight increase in fibrosis (from F0 to F1A).

No explanation could be found concerning the patient with no resolution of hepatocyte ballooning. Indeed, this patient lost significant weight and had decreased metabolic syndrome, insulin resistance (HOMA-IR: from 5.4 to 2.3) and ALT levels. Liver complications were also reduced, including hepatic steatosis (from S3 to S1), inflammation and fibrosis (from F2 to F0).

Interestingly, some studies with paired liver biopsies also report an improvement in the histopathological criteria for NASH in the short term (mean follow-up of 21.35 ± 4.5 months) [9, 11,13] and fibrosis [9,11,14,18]. Our study provides evidence for the beneficial effects of LRYGB on NASH features, including inflammatory foci, ballooning and fibrosis being reduced after a median follow-up period of 57 [44; 79] months.

We also found that hepatocyte apoptosis, as evaluated by serum K18 fragment had improved at 1 year after a LRYGB and remained low until the last follow-up (at 57 [44; 79] months). In our patients, this hepatocyte apoptotic marker was increased in patients with NASH (approximately four fold), which is in accordance with previous reports on overweight, obese and severely obese patients [36][37][32][38][39][40][41], and correlates with NAS (r= 0.549, *P*<0.001, *n*=41).

Taken together, these data suggest the use of this marker as a non-invasive tool to monitor the evolution of NASH after bariatric surgery. In accordance with this, Wai-Sun Wong *et al.* recently reported that the level of serum K18 fragment reflected disease activity in a prospective longitudinal study on overweight/obese patients undergoing paired liver biopsies at a follow-up time of 3 years [42]**.**

The improvement in hepatocyte death and reduction of inflammation after a LRYGB could prevent the progression of hepatic complications. Indeed, apoptotic hepatocytes are engulfed by Kupffer cells, which results in activation and inflammation. The activation of stellate cells by apoptotic bodies or by TGFβ from activated Kupffer cells then leads to liver fibrosis [43]. Further, a pan caspase inhibitor or overexpression of the anti-apoptotic Bcl2 protein reduced fibrosis in an animal model of NAFLD and fibrosis, respectively [44,45]. Because pharmacological therapy has only marginal and perhaps clinically irrelevant effects on NASH and

fibrosis, and in light of these results, the implications for the protective effect of LRYGB against the progression of obesity-related liver complications may become particularly relevant [46-47-48]**.**

Although the main weakness of the present study relies in the small size of the sample, the exhaustive preoperative and postoperative work-up and the paired liver biopsy allowed complete characterization of our patients with severe steatosis and NASH. We were thus able to demonstrate that the LRYGB results in the concomitant remission of systemic inflammation, insulin resistance and NASH features (steatosis, inflammation and hepatocyte apoptosis) in all patients at a median follow-up of 57 months. We also found a correlation between decreased serum levels of hepatocyte apoptotic markers (K18 fragment) and remission of NASH. These results should be confirmed in additional studies with a larger sample size and a longer follow-up (>6 years) to better understand the molecular mechanisms that are involved in the remission of obesity-related liver complications after LRYGB.

DISCLOSURES

The authors declare no conflicts of interest

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FIGURE LEGENDS

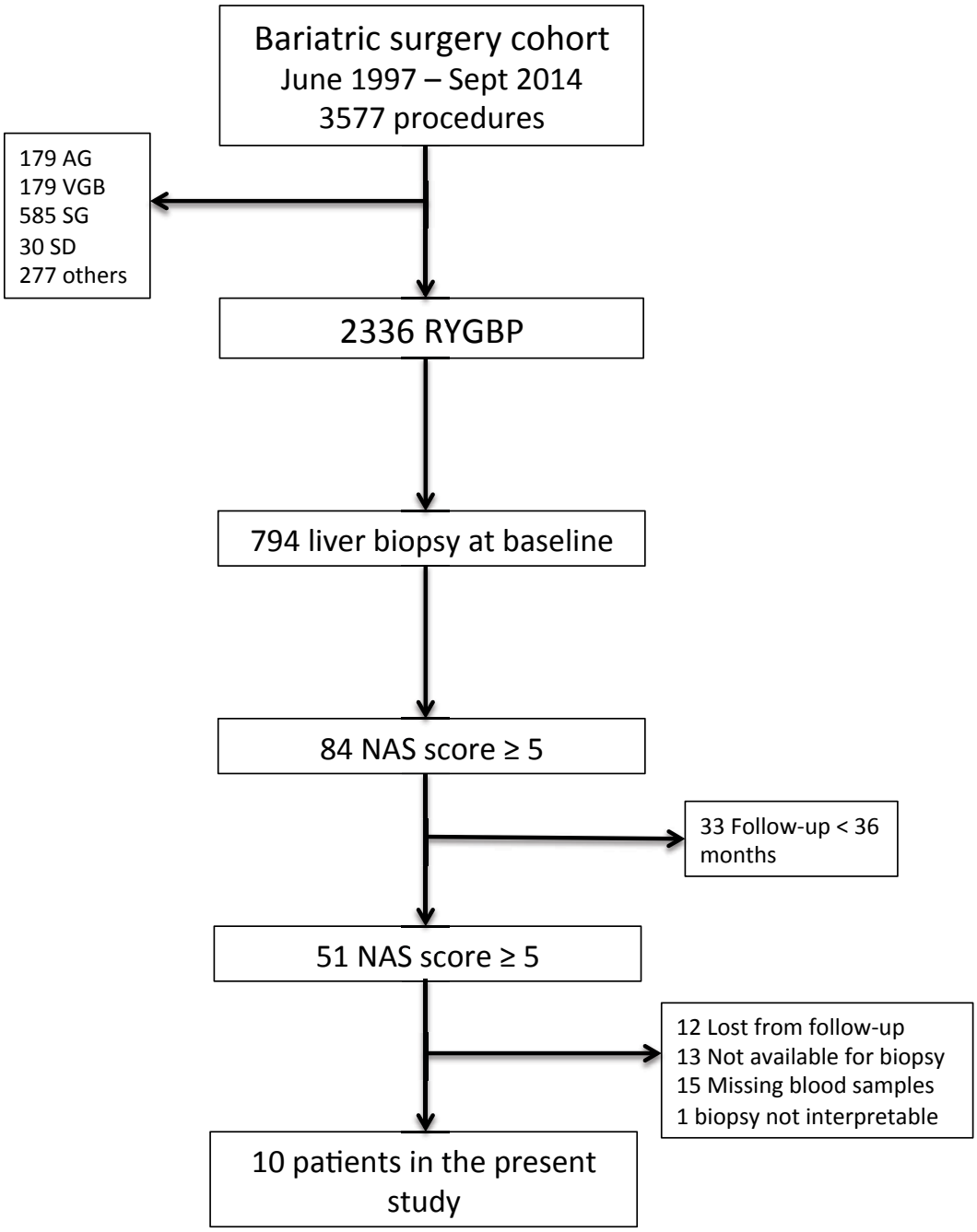

Figure 1: Flow chart of Nice bariatric cohort

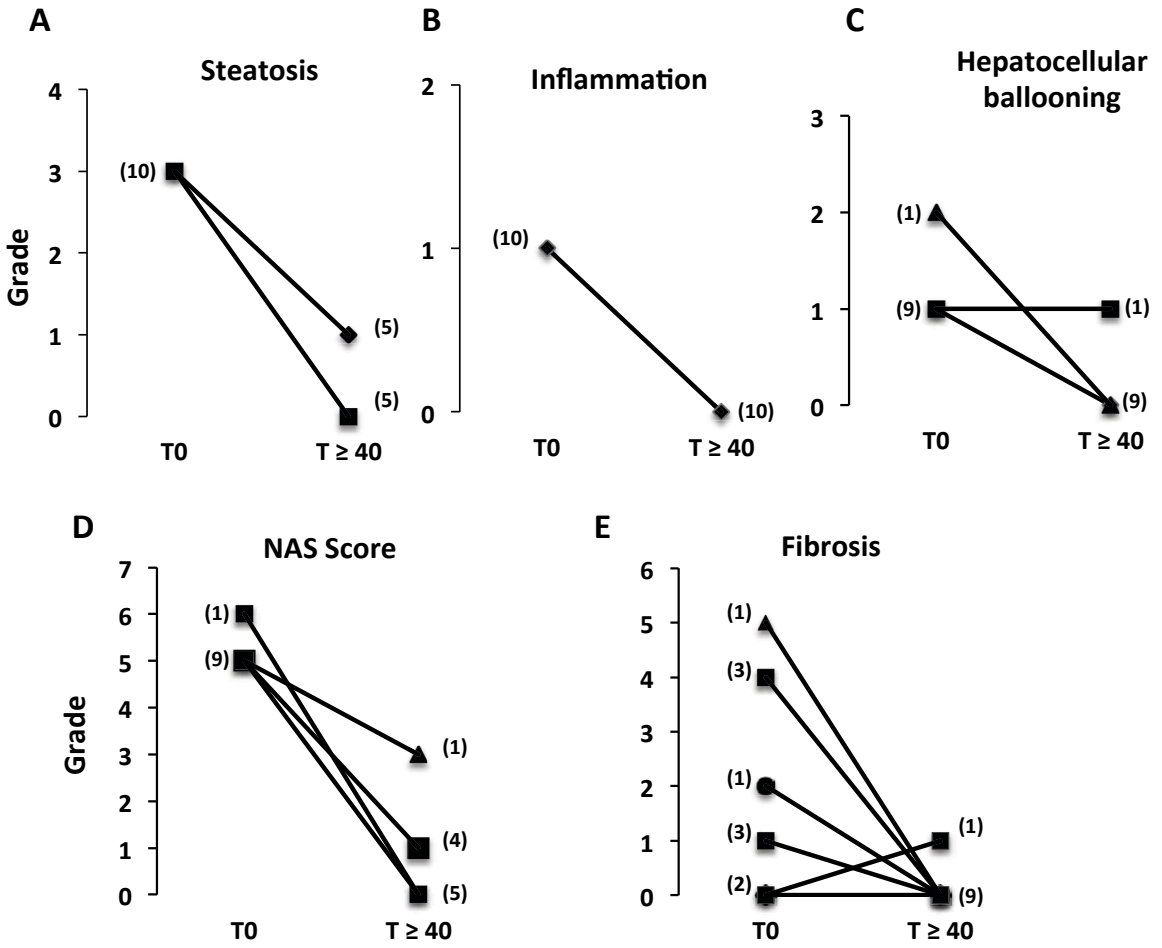

Figure 2: LRYGB in NASH patients improves hepatic steatosis and NAS in all patients, and hepatic inflammation and fibrosis in the large majority after a median follow-up of 57 months. Ten morbidly obese patients with biopsy-proven NASH underwent LRYGBP and had a second liver biopsy at a median follow-up period of 57 [44; 79] months after surgery. From the paired liver biopsies, steatosis **(A)**, inflammatory foci **(B),** hepatocellular ballooning **(C)** and fibrosis **(E)** were evaluated. **(D)** The NAFLD score (NAS) was evaluated as described in Materials and Methods. Fibrosis were semi-quantitatively evaluated: 0 = none, 1: perisinusoidal or periportal mild (1 A), 2= moderate (1B), 3: portal/periportal (1C), 4: perisinusoidal and portal/periportal, 5: bridging fibrosis, 6: cirrhosis. (*N*): number of patients.

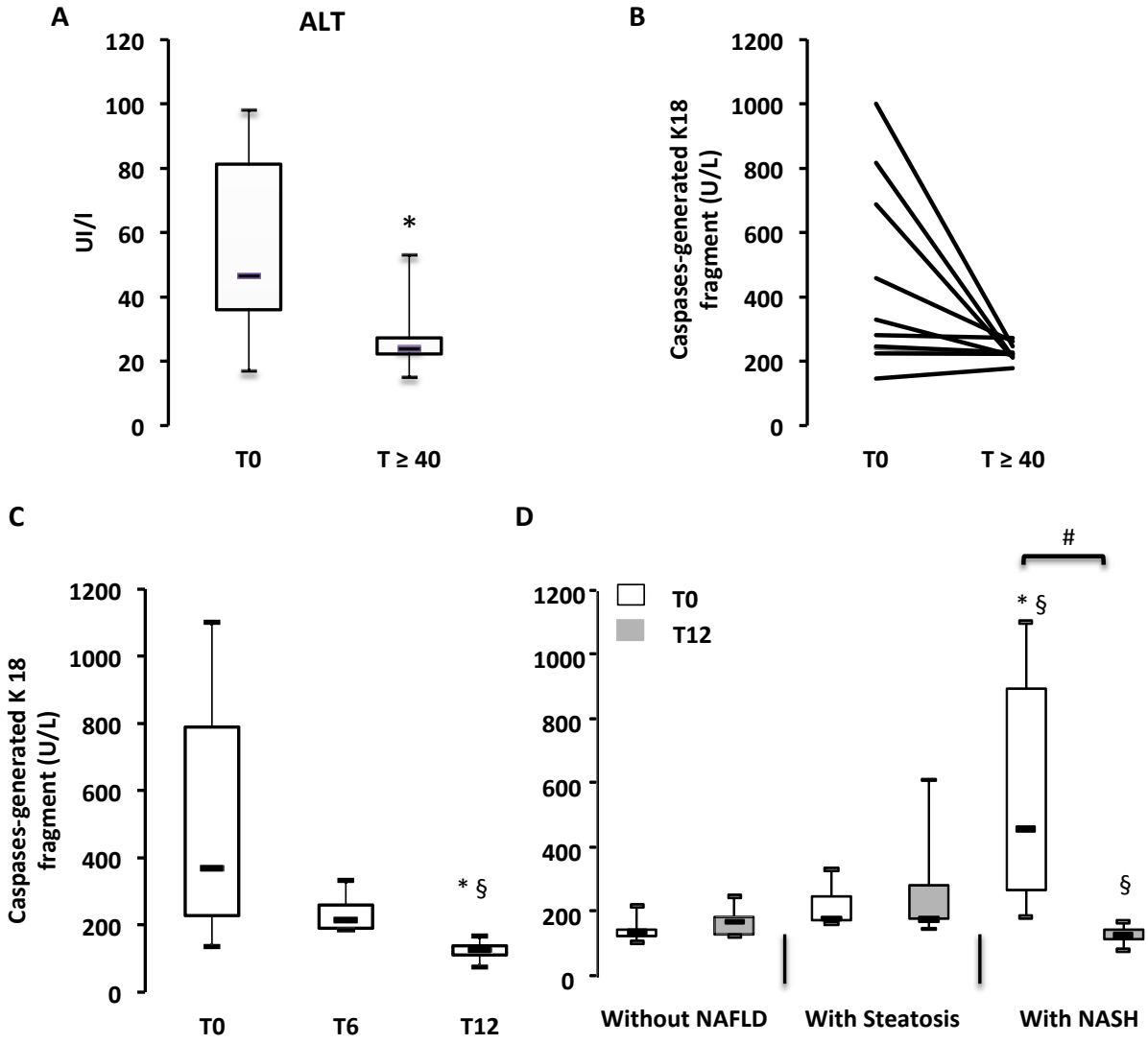

Figure 3: LRYGB improves liver injury and hepatocyte apoptosis in NASH patients after a median follow-up of 57 months. Serum levels of **(A)** alanine aminotransferase (ALT), and **(B)** a marker of hepatocyte apoptosis (caspase-generated keratin 18 fragment) (K18 fragment) were evaluated at baseline and at the median follow-up of 57 [44; 79] months after LRYGB in NASH patients. The levels of K18 fragment were also evaluated **(C)** at 6 months and at 1 year after a LRYGB and, **(D)** at baseline (T0) and 1 year (T12) after LRYGBP in three additional groups of patients without NAFLD (*n*=5), severe steatosis (*n*=7) or NASH (*n*=7). Results are expressed as the median [25th, 75th percentiles] **(A, C, D).** **P*<0.05, compared with baseline; $^{\$}$*P*<0.05, compared with 6 months follow-up; $^{\#}$*P*<0.05, compared with baseline values of NASH patients.

	T0	T ≥ 40	p
Number (M/F)	10 (1/9)	10 (1/9)	*ns*
Age (years) (median[Q1; Q3])	48 [33.8; 58.8]	53 [40.3; 64.3]	*ns*
Time after surgery (months) (median[Q1; Q3])		57 [44; 79]	
BMI (kg/m^2) (median[Q1; Q3])	41.9 [39.3; 44.8]	28.8 [24.7; 32.2]	*< 0.001*
Δ BMI (kg/m^2) (median[Q1; Q3])		13.3 [-15.9;- 9.3]	
Fasting glucose (mmol/l) (median[Q1; Q3])	6.3 [4.9; 8.4]	4.6 [4.2; 5.2]	*0.018*
Fasting insulin (mUI/l) (median[Q1; Q3])	20 [17; 30]	9 [8; 15]	*0.034*
HOMA-IR (median[Q1; Q3])	6.4 [3.7; 8.5]	2.3 [1.5; 3.0]	*0.006*
Diabetes (%)	4 (40)	0 (0)	*ns*
Metabolic syndrome (%)	7 (70)	2 (20)	*ns*
CRP (mg/dl) (median[Q1; Q3])	7.4 [5.6; 8.0]	0.6 [0.5; 1.4]	*0.001*

Table 1: Patients' demographics and biochemical parameters at baseline and after a >40-month follow-up period.

Body-mass index (BMI), Excess BMI loss (Δ BMI), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), C-reactive protein (CRP), not significant (*ns*), *p*: the Mann–Whitney test or Fisher's exact test.

Conclusion

Dans ce travail de thèse j'ai mis au point un modèle animal chez la souris de SG. Ce modèle a permis de montrer que d'autres mécanismes que la restriction alimentaire sont impliqués dans la perte pondérale mais aussi dans la rémission de l'insulinorésistance, de l'inflammation du tissu adipeux viscéral et surtout de l'amélioration des complications hépatiques de l'obésité. En perspective ce modèle peut être utilisé pour étudier les mécanismes d'action de la SG et oriente la recherche clinique vers les cibles thérapeutiques indépendantes de la restriction calorique.

Dans un deuxième travail ont été étudié les effets du RYGBP sur la NASH dans une cohorte de patients obèses morbides opérés d'une chirurgie bariatrique prospective avec une tissuthèque hépatique et une sérothèque. J'ai pu montrer que le RYGBP permet une rémission de la stéatose hépatique et de taux sériques de l'inflammation. En outre un marqueur sérique de la mort cellulaire, le M30, corrèle avec l'amélioration de la souffrance hépatocytaire. Bien que les effets à long terme du RYGBP sur la NASH doivent être plus largement caractérisés, ces résultats légitiment l'utilisation de cette opération chez les patients atteints de NASH.

Annexes

1. Laparoscopic sleeve gastrectomy as a revisional procedure for failed gastric banding: lessons from 300 consecutive cases.
Noel P, **Schneck AS,** Nedelcu M, Lee JW, Gugenheim J, Gagner M, Iannelli A.
Surg Obes Relat Dis. 2014 Mar 15. doi: 10.1016/j.soard.2014.02.045. [Epub ahead of print]

2. Preoperative 4-week supplementation with omega-3 polyunsaturated fatty acids reduces liver volume and facilitates bariatric surgery in morbidly obese patients.
Iannelli A, Martini F, **Schneck AS**, Ghavami B, Baudin G, Anty R, Gugenheim J.
Obes Surg. 2013;23:1761-5. doi: 10.1007/s11695-013-0942-y.

3. Bariatric Surgery and Liver Transplantation: a Systematic Review a New Frontier for Bariatric Surgery.
Lazzati A, Iannelli A, **Schneck AS**, Nelson AC, Katsahian S, Gugenheim J, Azoulay D.
Obes Surg. 2014 Oct 22. [Epub ahead of print]

4. A simple model to predict moderate to severe steatosis in morbidly obese liver donors.
Iannelli A, Martini F, Anty R, Tavana R, **Schneck AS**, Patouraux S, Gual P, Tran A, Gugenheim J. Liver Transpl *In press*

5. NASH chez le patient obèse sévère : une indication de la chirurgie bariatrique
Schneck AS, Anty R, Gugenheim J, Iannelli A
Diabète et Obésité - Octobre 2014 Volume 9 n°82

La Sleeve gastrectomie (SG) a connu un essor très important en France en augmentant exponentiellement avec la réalisation de 18,000 interventions en 2012("French National Hospital Database(Programme De Médicalisation des Systèmes d'Information – PMSI).) L'anneau gastrique (AGB) est une opération qui est encore pratiquée environ 6,000 fois par an en France, chiffre stable depuis 2007. Cette intervention est particulièrement sûre avec une mortalité pratiquement nulle. Cependant elle est associée à la perte pondérale la moins importante et à un taux considérable de complications à long terme qui mènent à l'ablation de l'AGB (Suter et al., 2006). L'échec de l'AGB est un problème avec lequel le chirurgien bariatrique se confronte souvent dans sa pratique courante. Les études initiales de la littérature sur les conversions d'AGB en SG avaient montré un taux augmenté de complications post-opératoires surtout sous la forme de fistule haute. Donc nous avons analysé les résultats de cette conversion dans une série homogène de patients. Nous avons trouvé qu'il n'y avait pas de différence significative sur le taux de fistule entre le groupe de patients opérés sans antécédent de chirurgie bariatrique et ceux avec un antécédent d'AGB. Ces résultats sont expliqués par un effet de la courbe d'apprentissage car les complications étaient survenues tout en début d'expériences et par la stratégie en deux temps comprenant la réalisation de l'ablation de l'AG et la SG avec délai minimum de trois mois.

L'analyse exhaustive des données de la littérature a confirmé l'effet de la stratégie en deux temps.

(*Laparoscopic sleeve gastrectomy as a revisional procedure for failed gastric banding: lessons from 300 consecutive cases. Noel P, Schneck AS, Nedelcu M, Lee JW, Gugenheim J, Gagner M, Iannelli A. Surg Obes Relat Dis. 2014 Mar 15)*

La NAFLD s'associe à une hypertrophie du foie qui est due à l'accumulation de triglycérides. Cette augmentation de volume, notamment des segments II et III hépatiques, peut gêner considérablement le geste chirurgical et être à l'origine de complications peropératoires telles que les plaies hépatiques et l'hémorragie qui en suit. En effet, le foie de stéatose est beaucoup plus fragile et a tendance à saigner lors de la manipulation chirurgicale. Les difficultés opératoires se traduisent aussi souvent par une mauvaise qualité de la chirurgie bariatrique due à l'impossibilité de réaliser la dissection de la région cardiale sous contrôle de la vue. La préparation à la chirurgie bariatrique est l'une des clés pour diminuer le risque de complication post-opératoire et pour optimiser la durée et la qualité de l'intervention chirurgicale. Les acides gras polyinsaturés oméga-3 ont des propriétés anti-inflammatoires. Une méta-analyse récente a montré leur efficacité dans la diminution de l'infiltration graisseuse du foie . Dans une étude pilote prospective, nous avons donc testé l'hypothèse que l'administration préopératoire d'oméga-3 pendant 4 semaines diminue les dimensions du lobe hépatique gauche mesurées à l'échographie. Les résultats de cette étude ont montré une diminution volumétrique des segments II et III de 20 % après le traitement par oméga-3 (de 598±97 à 484±118 cm^3) (p=0.002). Bien que devant être vérifiés dans une étude randomisée, ces résultats sont prometteurs, car il s'agit d'une stratégie de réalisation simple et non invasive. Une étude randomisée, contrôlée, en double aveugle et multicentrique va être soumise au prochain appel d'offre de Projet Hospitalier de Recherche Clinique (PHRC) régional.

(*Preoperative 4-week supplementation with omega-3 polyunsaturated fatty acids reduces liver volume and facilitates bariatric surgery in morbidly obese patients. Iannelli A, Martini F, Schneck AS, Ghavami B, Baudin G, Anty R, Gugenheim J. Obes Surg. 2013;23:1761-5.)*

Avec l'épidémie de l'obésité de plus en plus de patients obèses deviennent candidats à la transplantation hépatique. Cela est dû d'une part à l'augmentation de la prévalence de la cirrhose avec insuffisance hépatique liée à la NASH et d'autre part à l'augmentation des cancers primitifs du foie chez le sujet obèse avec NASH (Agopian et al., 2012). Plusieurs problèmes se posent pour les patients obèses. En effet, ces patients semblent accéder moins facilement à la transplantation hépatique (Segev et al., 2008) et les résultats de la transplantation hépatique pour cette population sont encore controversés (Perkins, 2007).

La chirurgie bariatrique est le seul moyen thérapeutique efficace sur l'obésité et ses comorbidités (Buchwald and Oien, 2013b). Elle a donc été proposée aux candidats à la transplantation hépatique et aux patients obèses transplantés hépatiques.

Nous avons fait une revue systématique de la littérature sur la chirurgie bariatrique et la transplantation hépatique. Elle montre que la plupart des études concernent des interventions de chirurgie bariatrique réalisées après la transplantation hépatique. De plus, la sleeve gastrectomie est l'opération la plus souvent proposée. La chirurgie bariatrique est faisable avant, pendant et après la transplantation hépatique, sans impact majeur sur le traitement immunosuppresseur. La morbi-mortalité de la chirurgie bariatrique est plus élevée dans cette population, mais reste acceptable.

(Bariatric Surgery and Liver Transplantation: a Systematic Review a New Frontier for Bariatric Surgery. Lazzati A, Iannelli A, Schneck AS, Nelson AC, Katsahian S, Gugenheim J, Azoulay D. Obes Surg. 2014 Oct 22.)

Avec l'épidémie de l'obésité et la pénurie de greffons, les transplanteurs hépatiques sont souvent confrontés au problème du choix d'un «organe limite». La stéatose associée à l'obésité représente une des principales limites à l'utilisation des greffons issus de

donneurs obèses. Une valeur seuil de 30% de stéatose est acceptée par la plupart des centres de transplantation hépatique. La mesure de la stéatose nécessite une biopsie qui rarement disponible la nuit dans les centres hospitaliers périphériques où a lieu le prélèvement d'organes. Le transplanteur doit donc accepter le greffon sur des données fournis par l'Agence de la Biomédecine. Nous avons mis au point un modèle qui permet de prédire un taux de stéatose > 30% en analysant notre cohorte prospective de patients obèses morbides opérés d'une chirurgie bariatrique pour lesquels nous disposions d'une biopsie hépatique, de données anthropométriques et biologiques. Ce modèle permet de prédire un taux de stéatose > 30% sur la base de 3 paramètres qui sont l'âge, le tour de taille et le taux sériques des alanine amino-transférases (ALAT) avec une sensibilité de 72% et une spécificité de 70%.

(*A simple model to predict moderate to severe steatosis in morbidly obese liver donors. Iannelli A, Martini F, Anty R, Tavana R, Schneck AS, Patouraux S, Gual P, Tran A, Gugenheim J. Liver Transpl In press)*

Une mise au point en français résume les principaux résultats de la chirurgie bariatrique chez les patients obèses morbides qui présentent une NAFLD.

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SURGERY FOR OBESITY AND RELATED DISEASES

Original article

Laparoscopic sleeve gastrectomy as a revisional procedure for failed gastric banding: lessons from 300 consecutive cases

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Abstract

Background: Laparoscopic adjustable gastric banding (LAGB) is a common bariatric procedure associated with a high rate of weight loss failure and/or complications in the long term. The objective of this study was to test the hypothesis that the conversion of failed LAGB into laparoscopic sleeve gastrectomy (LSG) is not associated with an increased risk of postoperative complications and leads to weight loss results that are comparable to those obtained with a primary LSG.
Methods: We retrospectively analyzed the results of a prospective series of 1360 LSG regarding patient demographics, the indication for revision morbidity, the percentage of excess weight loss, and the rate of postoperative complications.
Results: The primary LSG group contained 1060 patients and the LAGB to LSG group contained 300 patients. The rate of postoperative complications was 4.5% in the primary LSG group and 2% in the LAGB to LSG group. Two patients died in the LSG group (1 pulmonary embolus, 1 myocardial infarction). There was no significant difference with respect to the rate of leak, which was 1% in the LAGB to LSG group and 1.6% in the primary LSG group. There was a greater weight loss after primary LSG, mean % excess weight loss of 75.9% ± 21.4 at a mean interval of 29 ± 19.8 months, versus 62.6% ± 22.2 at a mean interval of 35 ± 24 months after LAGB to LSG ($P = .008$). There were 72.1% and 59.2% of patients available for follow-up after primary LSG at 24 and 60 months respectively, versus 69.3% and 55.4% after LAGB to LSG.
Conclusion: This study indicates that the risk of leak after LSG was not increased after conversion failed LAGB into LSG when performed as a 2-step procedure. (Surg Obes Relat Dis 2014;▮:00–00.)

Keywords: Failed gastric banding; Revision procedure; Laparoscopic sleeve gastrectomy

Laparoscopic adjustable gastric banding (LAGB) is a very common bariatric procedure, not only because it is a relatively simple and straightforward surgical technique, but also because it is associated with the lowest risk of immediate postoperative complications and mortality [1,2]. However, several studies have shown that gastric banding is associated with a high failure rate, either due to complications and/or insufficient weight loss [3,4]. A few surgical options exist to revise a failed gastric banding [5]. It is possible to replace the band with a new band in a very limited category of patients [6], but conversion into a

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1550-7289/

Roux-en-Y gastric bypass (RYGB) is considered by most as the procedure of choice [7]. Over the last few decades, the laparoscopic sleeve gastrectomy (LSG) has emerged as a third option [8,9]. However, this procedure has been associated with an increased risk of postoperative complications compared with a primary LSG [10,11].

To test the hypothesis that the conversion of failed LAGB into LSG is not associated with an increased risk of postoperative complications and leads to weight loss results that are comparable to those obtained with a primary LSG, we retrospectively analyzed the results of a prospective series of 1,360 consecutive LSG, of which 300 were conversion from a failed LAGB.

Methods

Data on LSG were extracted from a prospective database of morbidly obese patients undergoing bariatric surgery for morbid obesity according to the National Institute of Health consensus conference [12] between December 2005 and March 2013. All patients were informed of the risks inherent in primary and revisional bariatric surgery, as well as the potential benefits and alternatives to it, and signed a preoperative written consent for surgery.

Variables extracted from the database were age, gender, type of procedure (primary LSG versus conversion of failed LAGB to LSG), body mass index (BMI), indications for revision, postoperative complication and mortality, reintervention rate, length of hospital stay, and weight loss over time (excess weight loss [EWL], excess BMI loss, [EBL]). Patients were divided into 2 groups: primary LSG and LAGB to LSG. Three hundred patients undergoing LSG as a revisional procedure for failed gastric banding (LAGB to LSG group) were compared to the remaining 1,060 patients undergoing LSG as a primary procedure (primary LSG group).

The ideal weight in kilograms was calculated as follows: 50 + 2.3 * [(height in cm/2.54) - 60] for men and 45.5 + 2.3 * [(height in cm/2.54) - 50] for women [13]. Excess weight was calculated as the preoperative weight minus the ideal weight. Weight loss was expressed as the percentage of excess weight loss (%EWL) over time. The %EWL was calculated as follows: (preoperative weight - postoperative weight)/(preoperative weight – ideal weight) * 100)). Excess BMI was calculated as the preoperative BMI minus 25. Weight loss was expressed as the %EBL over time. The % EBL was calculated as follows: (preoperative BMI - postoperative BMI)/(preoperative BMI – 25) * 100)). LSG failure was defined as a % EWL < 50% beyond 1 year. Gastroesophageal reflux (GERD) was defined based on heartburn symptoms associated with endoscopically proven esophagitis. Conversion of LSG to laparoscopic RYGB was done in patients with GERD symptoms resistant to a proton pump inhibitor. Band erosion was defined based on upper gastrointestinal endoscopy that could identify the band in the lumen of the stomach.

Surgical technique of conversion of LAGB to LSG

All patients underwent a 2-step conversion procedure. First, the band was removed laparoscopically and a minimum 3-month interval was required before conversion to LSG. Patients were put in the French position with the surgeon standing between the patient's legs. A 3-port laparoscopic procedure was performed as previously described [14]. The ports included a 5-mm port for the 30° camera on the supraumbilical midline, 10 cm under the xiphoid and 2 cm to the left to avoid the round ligament, a 12-mm port in the right upper quadrant for the stapler (Echelon 60 Endopath, Ethicon EndoSurgery, Cincinnati, OH or EndoGIA 60 Tristapler, Covidien Surgical, Mansfield, MA) and a 5-mm port on the left midclavicular line. Occasionally, an additional 5-mm port was introduced to expose the stomach in case of a huge left liver lobe. The greater curvature of the stomach was freed starting 6-cm proximal to the pylorus up to the angle of His with a Harmonic scalpel (Ethicon EndoSurgery, Cincinnati, OH). The lateral border of the left crus was exposed to remove the entire gastric fundus, which is susceptible to dilation over time if left in place. No attempt was made to remove the residual scar tissue around the stomach. The gastric sleeve was constructed over a 37.5-Fr bougie (MIDSleeve, Dardilly, France) introduced along the lesser curvature up to the pylorus. The stomach was transected with green cartridges (Echelon 60 Endopath, Ethicon Endosurgery, Cincinnati, OH) or purple cartridges (EndoGIA 60 Tristapler, Covidien Surgical, Mansfield, MA) and the last transection was 5–10 mm lateral to the esophagus. No drains were left in place at the end of the procedure. Patients were started on oral fluids on the first postoperative day after an upper gastrointestinal series was negative for leak. Prophylaxis with subcutaneous low molecular weight heparin against deep venous thrombosis was initiated the next morning. Initially the protocol included enoxaparine 4000 IU twice a day, and then it was modified to enoxaparine 6000 IU/d for the remaining patients. They were discharged on postoperative day 3.

Statistical analysis

The data are presented as the mean ± standard deviation. The *t* test and χ^2 tests were used to compare the groups of patients. For all statistical tests, a P value < .05 was considered significant. All statistical analysis was done using NCSS 2007 (NCSS Statistical Software, Kayesville, UT).

Literature review

A search in PubMed MEDLINE (National Library of Medicine) was performed for English-language articles published from 2006, the year of publication of the first conversion of LAGB to LSG until January 2013, using the

Table 1
Patients' demographic characteristics in the LAGB to sleeve gastrectomy (SG) group compared to the primary SG

		LAGB to SG (n = 300)	SG (n = 1060)	*P* value
Age (yr)	Mean +/- SD	43.3 ± 11	40 ± 12	.0003
	Range	22–76	17–76	
Gender	Female / Male	261 (87%) / 39 (13%)	792 (74.7%) / 268 (25.3%)	.003
Weight (kg)	Mean +/- SD	117 ± 22.3	121 ± 23	.004
	range	75–220	65–240	
BMI (kg/m^{21}	Mean +/- SD	43 ± 7	44 ± 6.4	.012
	range	25–78	27–77	
Excess weight (kg)	Mean +/- SD	55.2 ± 20.2	59 ± 19	0.003
	range	7.3–156	13.6–157.8	

BMI = Body mass index; SD = standard deviation

key words, "laparoscopic", "obesity", "sleeve gastrectomy", and "gastric banding". Then, a search using the key words, "conversion", "redo surgery", and "bariatric" was performed. A full text copy of each publication was obtained. Only papers reporting on conversion of LAGB to LSG were considered. Any series on LSG with cases of conversion of LAGB to LSG was excluded. When multiple reports were found from a single institution, only the most recent report, with the highest number of patients, was considered. The following data were collected for each article: study type, number of patients, postoperative complications and incidence of leak, and interval of time between LAGB and conversion to LSG.

Results

There were 792 (74.7%) women and 268 (25.3%) men, with a mean age of 40 ± 12 (17–76) years in the primary LSG group and 261 (87%) women and 39 (13%) men, with a mean age of 43 ± 11 (22–76) years in the band to LSG group ($P = .0003$). Before surgery, mean initial BMI was 44 ± 6.4 (27–77) kg/m^2 and 43 ± 7 (25–78) kg/m^2 ($P = .012$), mean EW was 59 ± 19 (13.6–157.8) kg and 55.2 ± 20.2 (7.3–156) kg ($P = .003$) in the primary LSG group and in the LAGB to LSG group, respectively (Table 1). Indications for band removal were insufficient EWL for 185 patients (61.7%), complications such as pouch dilation for 97 patients (32.3%), band slippage for 15 patients (5%), and gastric erosion in 3 patients (1%).

Morbidity and mortality

Two patients died in the primary LSG group. One died of a pulmonary embolus on postoperative day 15 and 1 of myocardial infarction on postoperative day 12 (overall mortality .19%). There were no deaths in the LAGB to LSG group.

The rate of postoperative complications was 4.5% in the primary LSG group and 2% in the LAGB to LSG group (Table 2). There was no significant difference with respect to the rate of leak, which was 1% in the LAGB to LSG group and 1.6% in the primary LSG group. Four patients (1.3%) required reoperation in the LAGB to LSG group and 20 (1.9%) in the primary LSG group ($P = .55$) (Table 3). Three leaks in the LAGB to LSG group and 9 leaks and 1 abdominal abscess in the primary LSG group were treated by laparoscopic lavage and drainage. In 2 patients of the primary LSG group this procedure was followed by an endoluminal stenting. The remaining leaks in the primary LSG group were treated by an endoluminal stent (1 patient) or percutaneous drainage (7 patients). An endoluminal stent

Table 2
Complications in the LAGB to sleeve gastrectomy (SG) group compared to the primary SG

Complication	SG	LAGB to SG	*P* value
Leak	17 (1.6%)	3 (1%)	.47
Intra-abdominal abscess	4 (.38%)	0	.29
Stenosis	2 (.19%)	2 (.67%)	.168
Bleeding	19 (1.79%)	1 (.33%)	.069
Pancreatitis	1 (.09%)	0	.6
Humeral vein thrombosis	1 (.09%)	0	.6
Portal thrombosis	1 (.09%)	0	.6
Portal phlebitis	1 (.09%)	0	.6
Twist	1 (.09%)	0	.6
Pleural effusion	1 (.09%)	0	.6
Total	48 (4.53%)	6 (2%)	.055

Table 3
Reoperation rate in the LAGB to sleeve gastrectomy (SG) group compared to the primary SG

Complication		LAGB to SG n (%)	SG n (%)	*P* value
Leak		3 (1%)	17 (1.6%)	.47
	Reoperation	3 (100%)	9 (52.94%)	
Intra-abdominal abscess		0	4 (.38%)	.29
	Reoperation	0	1 (25%)	
Stenosis		2 (.67%)	2 (.19%)	.168
	Reoperation	1 (50%)	0	
Bleeding		1 (.33%)	19 (1.79%)	.069
	Reoperation	0	10 (52.63%)	

was put in place in 2 patients after laparoscopic lavage and drainage in the primary LSG group. Fig. 1 shows the distribution of the leaks over time for the LAGB to LSG group and the primary LSG group. All 3 cases of leaks in the revisional group occurred within the first 30 cases and were during the first 150 cases of the whole series. The distribution of the leaks in the primary group was spread over the first 600 cases and no more leaks were recorded thereafter.

Furthermore, 10 patients underwent laparoscopic surgical exploration for bleeding in the primary LSG group and 1 stenosis was converted to RYGB laparoscopically after failed endoscopic dilation in the LAGB to LSG group. The second stenosis in the LAGB to LSG group was treated by endoscopic dilation. The 2 stenosis in the primary LSG group were treated by an endoluminal stent. Overall, an endoluminal stent was put in place in 2 patients in the revisional LSG group and in 5 patients in the primary LSG group ($P = .8$). No patient complained of GERD at follow-up visits. No conversion to open surgery was required in the entire series.

Weight loss

Weight loss after surgery was different in the 2 groups. The primary LSG group had a mean BMI of 28 ± 5.9 (17.7–51.7) kg/m^2, a mean %EWL of 75.9 ± 21.4% (16.5–39.4), and % EBL of 88 ± 26% (18–169.8) at a mean interval of 29 ± 19.8 (1–92) months. The LAGB to LSG group had a mean BMI of 30 ± 4.9 (22.4–44.5) kg/m^2, a mean %EWL of 62.6% ± 22.2% (24–100.7), and % EBL of 72.4 ± 25.8% (26.5–121) at a mean interval of 35 ± 24 (1–90) months ($P = .008$) (Fig. 2). There were 72.1% and 59.2% of patients available for follow-up after primary LSG at 24 and 60 months, respectively, versus 69.3% and 55.4% after LAGB to LSG. There was no statistical difference in the rate of failure beyond 2 years follow-up in the 2 groups (Table 4).

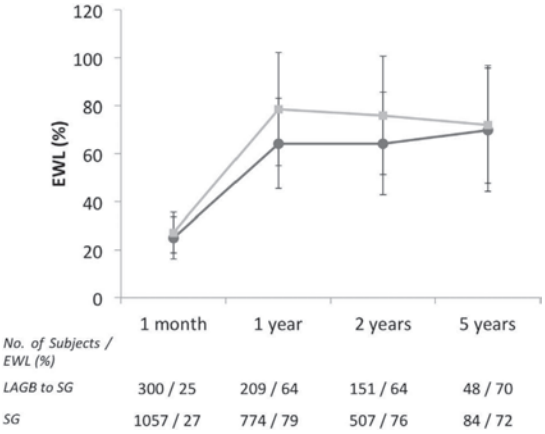

Fig. 2. Postsurgical weight loss. Mean excess weight loss (EWL) (%) in the LAGB to sleeve gastrectomy (SG) group (round mark) compared to the primary SG group (square mark) during their follow-up periods.

Discussion

An increasing number of patients with LAGB will benefit from a second bariatric procedure for insufficient excess weight loss or because of complications related to the band [4]. This study demonstrates that LSG is a valuable option in case of LAGB failure, as it results in a similar rate of postoperative complications and weight loss compared with primary LSG. LSG has been proposed as an alternative to more complex surgical procedures such as the RYGB or the duodenal switch. The Achilles' heel of the LSG is the risk of a leak that may occur in up to 5% of the cases [15]. A history of LAGB is considered by most to increase the risk of leak for several reasons (Table 5). The scar tissue around the LAGB may impair stapling and interfere with the healing of the stapled stomach. Furthermore, the LAGB may also jeopardize the tiny vascular supply of the esophagogastric junction where most leaks occur. Our policy consists in removing the gastric band first and doing the LSG after an interval of at least 3 months. The rational underlying the 2-step approach is that the scar tissue around the stomach progressively disappears once the band has been removed, rendering the LSG technically easier and safer. Indeed, we believe that the regression of the thick scar tissue around the stomach diminishes the risk of staple line failure due to incomplete staple closure that, in turn, may be at the origin of the leak. The 2-step approach also facilitates the undoing of the gastrogastric tunnel at the time of band removal, eliminating the risk of stapling over a plicated stomach and renders the gastric fundus mobilization easier at the time of the second step. As there is no consensus on the timing of conversion after failed LAGB, i.e., band removal and secondary conversion (2-step approach) versus

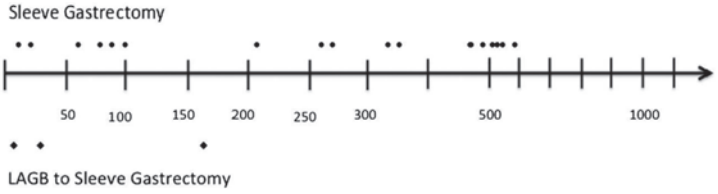

Fig. 1. Distribution of the leaks over time for the LAGB to sleeve gastrectomy (SG) group and the primary SG group.

Table 4
Studies reporting revisional surgery after LAGB

Study	1-step n of patients /n of leaks (%)	2-step n of patients /n of leaks (%)	Mean interval (mo)	Complications rate n (%)	Leak rate n (%)
Bernante et al. [16]	8	0	NA	0	0
Tucker et al. [19]	10 / 1 (10)	0	NA	2 (20)	1 (10)
Acholonu et al. [17]	13 / 1(7.7)	2	12	2 (13.3)	1 (6.7)
Berry et al. [18]	9	0	NA	0	0
Dapri et al. [20]	27	0	NA	1 (3.7)	0
Iannelli et al. [31]	0	41 / 1 (2.4)	3	5 (12.2)	1 (2.4)
Uglioni et al. [22]	29	0	NA	1 (3.4)	0
Foletto et al. [23]	36 (NR)	16 (NR)	3	4 (7.7)	1 (1.9)
Gagnière et al. [24]	14 / 2 (14.3)	17 / 3 (17.6)	6	10 (32.3)	5 (16.1)
Goitein et al. [21]	26 / 2 (7.7)	20	24	3 (6.5)	2 (4.3)
Jacobs et al. [25]	26	0	NA	0	0
Berende et al. [11]	15 / 5 (33.3)	13	3	9 (32.1)	5 (17.9)
Rebibo et al. [26]	46	0	NA	4 (8.7)	2 (4.3)
Yazbek et al. [27]	90 / 5 (5.6)	0	NA	8 (8.9)	5 (5.5)
Kahn et al. [29]	17 / 2 (11.8)	3	3	3 (15)	2 (10)
Alqahtani et al. [28]	56	0	NA	2 (3.6)	0
Present series, 2013	0	293 / 3 (1)	3	6 (2.1)	3 (1)
Total	422 (18)	405 (7)		60 (7.3)	28 (3.4)
Mean leak rate	4.3 %*	1.7 %*			

NA = not applicable; NR = not reported.
Only studies reporting clearly which approach (1-step or 2-step) was chosen were included in the review of the literature.
*$P < .05$

band removal and simultaneous conversion (1-step approach) an exhaustive literature review to compare the 2 alternative approaches with regard to the rate of post-operative complications and leaks was undertaken. There were 16 studies reporting conversion of failed LAGB to LSG with either a 1-step or a 2-step approach. There were 15 studies reporting on the 1-step approach with a total number of 422 patients and a leak rate of 4.3%. There were 8 studies, including the present series, reporting on the 2-step approach with a total number 405 patients and a leak rate of 1.7%. This data indicates that the 2-step approach may reduce the risk of leak ($P = .033$) (Table 4) [10,11,16–29].

Recently Rebibo et al. [26] reported comparative rates of leak in patients undergoing simultaneous band removal and LSG (4.8%) compared with patients undergoing LSG on previously nonoperated stomach (4.2%). However, the leak rate recorded in the present series of 1% is 4 times lower than the leak rate reported by Rebibo et al. [26], Alqahtani et al. [28] reported a series of 56 patients undergoing the 1-step approach with no leaks, compared to 128 patients undergoing primary LSG (1 leak).

The frequency of leaks decreased over time, consistent with a strong learning curve effect [30]. The refinement of technical details, including the interval of time between the staple closure and firing, avoiding cross stapling and a looser calibration of the gastric tube to avoid lateral traction may account for the low rate of leak recorded in this study in both the LAGB to LSG and the LSG groups. This indicates that the phenomenon of leak cannot be explained solely by the fact that the LSG transforms the stomach into a tube with increased intraluminal pressure; some technical issues are probably also involved. Indeed, Parikh et al. [30] recently investigated the role of bougie diameter as a risk factor for leak and found that a diameter smaller than 40Fr was associated with an increased risk of leak. Although a 36Fr was used in the present series, the tube was used to guide the gastric stapling without lateral traction on the stomach, resulting in a loose calibration of the plasty. No staple line reinforcement was used in this series.

The difference in the EWL between the 2 groups recorded at 1 and 2 years after surgery was no more significant than 5 years after surgery. This difference corresponded to a significant difference in the rate of weight loss failure between the 2 groups (Table 5). Interestingly, the rate of failure is stable in the LAGB to LSG group at about 25% and increases overtime in the primary LSG group and becomes identical at 5 years. This tendency in weight loss failure may account for the differences observed between the weight loss curves at 1 and 2 years that are no more different at 5 years (Fig. 2). The most plausible explanation relies in the fact that the LAGB to LSG group includes patients that evolve more rapidly toward the failure

Table 5
Failure rate (% EWL < 50%) in the LAGB to sleeve gastrectomy (SG) group compared to the primary SG

	LAGB to SG (%)	SG (%)	*P* value
1 yr	26.7	7.3	.001
2 yr	27.9	12.6	.028
5 yr	23.1	25	.865

Percentage of excess weight loss (%EWL).

as they have already experienced the effect of surgery-induced restriction and develop eating strategies to overcome the effects of surgery. These data show that LSG as a revisional procedure for failed LAGB most probably gives the same anatomic results as a primary LSG. In other words, the potential risk of leaving part of the gastric fundus that may be responsible for a dilation of the gastric tube with a consequent weight regain seems to be minimal [31].

Although this study reports the largest series of LSG for failed gastric banding, there are 2 limitations. First, the anticoagulation protocol was also modified during the study period and it probably accounted for the high rate of staple line bleeding that required laparoscopic surgical exploration. Second, the hypothesis that splitting the procedure into 2 steps to reduce the rate of complication was chosen only on the basis of our review of the literature. We did not have a control group of patients undergoing a 1-step revisional LSG. All of these issues should be addressed in a large randomized trial with sufficient statistical power to define precise guidelines to adopt for patients undergoing conversion of a failed LAGB to LSG.

Conclusion

This study indicates that the conversion of failed LAGB to LSG is a safe and effective procedure. Data from the present series and those published in the literature are in favor of a 2-step approach with a minimum interval of 3 months between the 2 steps to the reduce the risk of leak associated with the LSG.

Disclosures

Michel Gagner, M.D., F.R.C.S.C., F.A.C.S., declares the following conflict of interests: Honorarium (Speaker's bureau): Ethicon Endosurgery, GORE, Covidien, MID, Transenterix, Boehringers laboratories, Cinemed; Equity: Transenterix. The other authors declare no conflict of interest.

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ORIGINAL CONTRIBUTIONS

Preoperative 4-Week Supplementation with Omega-3 Polyunsaturated Fatty Acids Reduces Liver Volume and Facilitates Bariatric Surgery in Morbidly Obese Patients

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Abstract
Background Non-alcoholic fatty liver disease (NAFLD) is a very common condition among obese patients that may lead to the enlargement of the liver, that in turn impairs the access to the gastro-esophageal junction during laparoscopic bariatric surgery. Omega-3 polyunsaturated fatty acids (Ω-3 PUFAs) supplementation has been shown to reduce nutritional hepatic steatosis. The aim of this study was to assess the effects of a 4-week course of oral Ω-3 PUFAs supplementation on the volume of the liver.
Methods 20 morbidly obese patients were administered oral Ω-3 PUFAs (1,500 mg daily) for 4 weeks before undergoing the laparoscopic Roux-en-Y gastric bypass (LRYGBP) without any dietary restriction. The volume of the left hepatic lobe was estimated by liver ultrasonography at baseline and at the end of treatment. The degree of difficulty to access the gastro-esophageal junction was appreciated subjectively by the operating surgeon.
Results All patients completed the study and no side effect was reported. The mean volume of the left hepatic lobe decreased by 20 % from 598±97 to 484±118 cm^3 after the treatment (p=0.002). The access to the gastro-esophageal junction was reported as simple, with easy retraction of the left hepatic lobe by the operating surgeon in all cases.
Conclusions This study demonstrates that a 4-week course of oral Ω-3 PUFAs supplementation results in a significant reduction in liver size that facilitates the LRYGBP.

Keywords Morbid obesity · Non-alcoholic fatty liver disease · Bariatric surgery · Liver volume · Omega-3 polyunsaturated fatty acids · Laparoscopic Roux-en-Y gastric bypass

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Introduction

Morbid obesity is the most significant risk factor for the development of non-alcoholic fatty liver disease (NAFLD), a term encompassing a spectrum of liver diseases ranging from simple steatosis (non-alcoholic fatty liver [NAFL]), to non-alcoholic steatohepatitis (NASH) [1–3], that sometimes

can progress to cirrhosis and hepatocellular carcinoma [4–6]. According to the "two-hit" hypothesis, insulin resistance and visceral obesity increase the intrahepatic triglyceride content, culminating in NAFLD, which is considered as a relatively benign condition. A correlation between steatosis, body weight and body mass index (BMI) has been demonstrated in several studies [7–9]. In a minority of patients a second hit in the form of oxidative stress and inflammation ensues, fuelling cell damage and fibrosis (NASH). In concomitance with the epidemic of obesity, NAFLD is emerging as a formidable health burden and an increasingly common cause of cirrhosis [2, 10]. NAFLD is extremely common among patients undergoing bariatric surgery, ranging from 84 % to 96 % as diagnosed by liver biopsy [7, 11, 12]. NASH is present in 25 % to 55 % of these patients, liver fibrosis in 34 % to 47 %, while 2 % to 12 % of patients have bridging fibrosis or cirrhosis [7].

The fatty enlargement of the left lobe of the liver may impair the adequate visualization of the gastro-esophageal junction in morbidly obese patients undergoing bariatric surgery. The fatty liver bleeds easily and the retraction necessary to expose the operating field may lead to inadvertent fracture of liver parenchyma. Technical difficulties due to an enlarged liver can lead to conversion to an open procedure or even to postpone the planned operation [13, 14]. It has been shown that preoperative weight loss in morbidly obese patients reverses the fatty changes of steatohepatitis, improving the functional liver parameters and reducing the liver size [7, 14–19].

Low-calorie diets and very low-calorie diets have therefore been used to reduce the size and fat content of the liver before bariatric surgery [14, 16, 17, 19, 20]. These studies showed a 5–19 % reduction in liver size, a 40–43 % reduction in intrahepatic fat, and a significant correlation between changes in liver volume and fat content [16, 19].

The intragastric balloon also represents an interesting alternative to induce a preoperative weight loss and a consequent reduction in the volume of the liver as demonstrated by Frutos et al. [18] that showed a mean reduction of 32 % in liver volume with an intragastric balloon over 6 months before LRYGBP in superobese patients (BMI ≥50).

The Ω-3 PUFAs, derived from exogenous sources such as fish oil, flaxseeds and olive oil, have a beneficial impact on most of the cardio-metabolic risk factors by regulating gene transcription factors [21–29]. Furthermore, Ω-3 PUFAs influence both lipid metabolism and insulin sensitivity. In addition to an enhancement of hepatic beta-oxidation and a decrease in the endogenous lipid production, Ω-3 PUFAs determine a significant reduction of the expression of pro-inflammatory molecules and oxygen reactive species. Both animal models and human intervention trials showed a beneficial effect of Ω-3 PUFAs on the severity of NAFLD as expressed by laboratory parameters and imaging measurements [30–37].

However, in spite of the well-known effects of Ω-3 PUFAs on NAFLD, there is no report in the literature on their use in morbidly obese patients to reduce the size of the liver before bariatric surgery. The aim of this study was to determine whether a 4-week course of oral Ω-3 PUFAs supplementation without dietary restriction before bariatric surgery could reduce the liver volume, rendering thus surgery easier and safer.

Materials and Methods

Between February and July 2012, 20 patients scheduled for LRYGBP according to the National Institutes of Health (NIH) [38] criteria were recruited from our bariatric surgery programme to participate in the present study. There were 18 females and two males with a mean age of 39 years (range 22–63) and a mean BMI of 42 kg/m^2 (range 37–51). All patients with BMI <40 presented at least one obesity-related comorbidity. The history of morbid obesity dated from 5 to 38 years.

All patients were administered orally Ω-3 PUFAs 1,500 mg (Epacaps®: Nycomed Pharma-CH; composition: fish oil (w) 750 mg, Ω-3 fatty acids: eicosapentaenoic acid (EPA) (w) 135 mg, docosahexaenoic acid (DHA) (w) 90 mg, Excip. pro caps) daily for 4 weeks before surgery without any dietary restriction.

Liver ultrasonography (US) was performed in all subjects at baseline and after the 4-week treatment course. A single trained operator carried out all scans using a Siemens Acuson Sequoia. Surgery was scheduled immediately after completion of Ω-3 PUFAs treatment. The volume of the left hepatic lobe was calculated on the basis of the following measures: transversal and supero-inferior axis, and the middle part of the antero-posterior axis ("thickness"), assuming that its shape was close to a half-rectangular parallelepiped.

The results are presented as means ± standard deviation. Statistical analysis was performed using SPSS V.20 statistical software. For continuous parametric data, means and SD, Student's *t*-test was used. A p value <0.05 was considered statistically significant.

Results

All 20 patients receiving Ω-3 PUFAs showed a good compliance to the supplementation and completed the study. A moderate fishy aftertaste was noted by most patients, which was well tolerated. No side effect was reported.

The volumes of the left hepatic lobe were estimated between 448 and 760 cm^3 (mean: 598±97 cm^3) before treatment and between 240 and 680 cm^3 (mean: 484±118 cm^3) after treatment (p=0.002). No direct relation was found between the volume of the left hepatic lobe at baseline and the BMI or the duration of the obesity. The mean

relative reduction of the volume of the left liver lobe was estimated at 20 % (range 5–32 %) (Fig. 1).

Although no objective assessment could be made during the surgical procedure, the operating surgeon reported that in all cases the access to the gastro-esophageal junction was simple, and the liver could be easily retracted. No bleeding from the liver was recorded.

Discussion

Obesity is considered to be a major public health problem, particularly, but not exclusively, in the Western world, with a rising global prevalence [39, 40]. Bariatric surgery has proved to be the most effective mean to achieve significant and persistent weight loss in morbidly obese patients [41]. Several studies have shown that up to 90 % of these patients

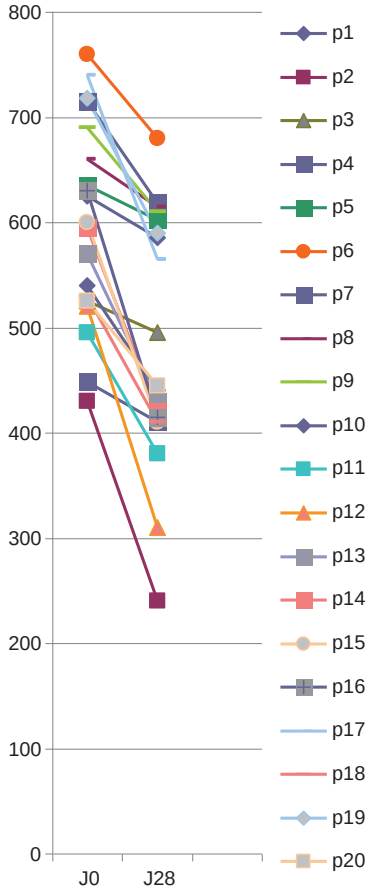

Fig. 1 Baseline and changes in estimation of the volume of the left hepatic lobe before and after a 4-week course of oral Ω-3 PUFAs supplementation

suffer from NAFLD [7, 11, 12], that represents the most important cause of chronic liver disease and a major independent cardiovascular risk factor [42]. As a definite treatment is lacking, weight loss by lifestyle therapy including diet and exercise is currently the primary treatment for NAFLD [32, 35, 37, 43]. Weight loss has been shown to improve liver enzymes [44–46], decrease plasma triglycerides [44, 46, 47] and the fat content of the liver, as measured by magnetic resonance spectroscopy (MRS), US or direct histological evaluation [47–49].

LRYGBP is a technically challenging procedure that is prone to surgical complications. A huge fatty liver may impair the exposure of gastro-oesophageal junction further complicating this already complex surgical procedure [13, 14].

Various dietary approaches have been reported to be effective in reducing the volume and the fat content of the liver that, in turn, facilitates bariatric surgery [14, 16, 17, 19, 20]. However, the dietary approach was associated with rate of failure of 20 % in the study of Benjaminov et al. [16] and 13 % in the study of Lewis et al. [19] due to incapacity of patients to complete the preoperative dietary regimen.

A growing interest has recently risen concerning the therapeutic potential of Ω-3 PUFAs in NAFLD. Several studies in the animal showed that Ω-3 PUFAs depletion can promote steatosis and insulin resistance. On the contrary, Ω-3 PUFAs supplementation is effective in preventing, and also in reversing, hepatic steatosis, by inducing a reduction in lipogenic genes expression, improving glycemic control, insulin levels and insulin sensitivity, reducing the oxidative stress, and exerting an anti-inflammatory effect [31, 35, 37]. Indeed, there is strong evidence that Ω-3 PUFAs supplementation reduces nutritional hepatic steatosis in adults [30, 32–37]. Although the ideal method to quantify liver steatosis is liver biopsy the invasiveness of this diagnostic tool limits its wide application in clinical studies and US, in most cases, and MRS, in only a few cases, are the diagnostic modalities used to quantify changes in liver fatness [30, 32–37]. Liver US analysis is currently thought to provide reliable information on hepatic steatosis and liver volume in experienced hands [50]. The impact of Ω-3 PUFAs on NASH histopathology has only been assessed in a subset of patients in a open-label trial by Tanaka et al. that demonstrated a significant improvement in laboratory markers of hepatic oxidative stress and decreased liver steatosis, inflammation and fibrosis [51].

Since several studies have clearly demonstrated that a large proportion of excess liver size in obesity is attributable to increased fat content of the liver [16, 19], our working hypothesis was that a Ω-3 PUFAs supplementation before bariatric surgery could lead to shrinkage of the liver even in the absence of any alimentary restriction. Indeed, as dietary Ω-3 PUFAs supplementation does not require any calorie restriction, has few side effects and limited costs, it represents a simple and practical alternative to more complex preoperative

dietary regimens that imply patients' compliance [32, 35, 37, 52]. In relation to the cost, the average price of a 4-week course of Ω-3 PUFAs at a daily dose of 1,500 mg is about €70–90, which is by far less expensive than most very low-calorie diets that cost €80–150 per week.

In this study, a 4-week preoperative course of Ω-3 PUFAs supplementation led to a mean reduction of 20 % of the baseline volume of the left hepatic lobe. This was associated with an easy exposure of the gastro-esophageal junction in all cases as subjectively reported by the operating surgeon and no case of bleeding from the liver.

Parker et al. [32] reported that Ω-3 PUFAs benefits are seen with a daily dose of 830 mg. Other studies reported a substantial reduction in all-cause and cardiovascular mortality with a daily dose of 1,000 mg of Ω-3 PUFAs [21–29]. We chose an increased daily dose of 1,500 mg of Ω-3 PUFAs given the short course of treatment.

The duration of low-calorie and very low-calorie diets varies in the literature between 2 and 12 weeks, with a rate of patients' exclusion from the studies which increases in parallel with the rising in time [14, 16, 17, 19, 20]. Our choice of a short 4-week supplementation aimed to prevent patients' withdrawal. In retrospect, we believe this length was optimal since it allowed satisfactory results being tolerated by all patients.

Our choice of US for the estimation of the volume of the left hepatic lobe instead of other imaging techniques as CT or magnetic resonance imaging was dictated by its easy availability, rapidity and the absence of radiation.

We acknowledge some methodological limitations including the reduced number of patients, the lack of a control group and of the evaluation of liver steatosis on imaging. Nevertheless, we could demonstrate that the volume of the left liver lobe as estimated on US decreased with a short preoperative course of Ω-3 PUFAs without any caloric restriction in morbidly obese patients. These data should be confirmed in a larger randomized trial in order to validate this strategy.

Conflict of interest All the authors declare that they have no conflict of interest.

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REVIEW ARTICLE

Bariatric Surgery and Liver Transplantation: a Systematic Review a New Frontier for Bariatric Surgery

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Abstract This study aims to conduct a systematic review on bariatric surgery (BS) for patients in the setting of liver transplantation (LT). A literature review was conducted on the PubMed, Embase, and Cochrane Library databases. Studies in the English language on adults reporting on BS prior to, during, or after LT were included. Eleven studies with 56 patients were retrieved. Two studies reported on BS before, two during, and seven after LT. Sleeve gastrectomy was the most common procedure, followed by Roux-en-Y gastric bypass, biliopancreatic diversion, and gastric banding. The overall mortality rate was nil in the early postoperative period and 5.3 % in the first postoperative year. The reoperation rate was 12.2 %. Obesity surgery seems feasible in this population, but mortality and morbidity are higher.

Keywords Bariatric surgery · Obesity · Liver transplantation · Sleeve gastrectomy · Metabolic syndrome · Non-alcoholic steatohepatitis

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Introduction

Obesity is reaching epidemic proportions worldwide, and the World Health Organization estimates that in 2008, half a billion adults are obese worldwide, but some authors [1] suggest that probably more than two billion adults are currently overweight or obese. Obesity is a complex disease that compromises several organs including the liver in the form of non-alcoholic fatty liver disease (NAFLD) that may progress from simple steatosis to non-alcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma [2]. As a consequence, concommitant with the epidemic of obesity, a major increase in NAFLD has been recorded in Western countries, reaching an estimated prevalence between 10 and 24 % [3] in the general population and 57.5 % [4] and 74 % [5, 6] in obese persons. Moreover, the progression of NAFLD to NASH has been reported in up to 42 % of cases [7], accounting for the growing indication for liver transplantation (LT) for NASH, going from 1.2 to 9.7 % in the last 10 years in the USA. Hence, NASH has become the third most common indication for LT [7] and epidemiological projections for the next decade indicate that this trend will continue and this pathology will probably become the most

common cause of liver failure requiring LT [8, 9]. Nevertheless, the increase in the prevalence of obesity among candidates for LT is not without concern, because obese patients seem to have a reduced access to LT [10] and the real outcome after LT for this specific population is still controversial [11].

Bariatric surgery (BS) has been proven to be the only effective treatment for morbid obesity, leading to a significant loss of weight and reduction in obesity-related comorbid conditions such as hypertension, diabetes, sleep apnea, dyslipidemia, and NAFLD that are maintained over the long term [12]. For this reason, BS has been proposed for candidates for LT as well as transplanted patients. Different approaches have been used concerning the timing of BS and LT: obesity surgery has been practiced before, during, and after the transplant. The aim of this study is to review all the studies of BS associated with LT.

Methods

Search Strategy

We conducted a systematic review on the PubMed, Embase, and Cochrane Library databases, adhering to the PRISMA statement.

The search was conducted in September 2013 and was not limited to any date range. We used the following as search terms: "liver transplantation," "bariatric/obesity surgery," "sleeve gastrectomy," "gastric banding," "gastric bypass," and "biliopancreatic diversion."

Inclusion Criteria

The data search was restricted to studies reporting on BS associated with LT in adults submitted in English. No limit concerning the timing of BS, before, during, or after LT, was applied.

Two authors independently reviewed the titles and abstracts of the references retrieved (Andrea Lazzati and Antonio Iannelli). The full text of all potentially relevant studies was analyzed for eligibility. Information from each study was extracted using a standardized data extraction form. Authors were contacted as appropriate.

Data Extraction

After inclusion, we retrieved the following variables from each study: year of publication, number of patients, type of bariatric procedure, patients' characteristics at LT and at BS (gender, age, body mass index), indication for LT, type of surgical approach, surgical complications, and mortality for LT and BS. Outcomes considered were weight loss, obesity-related comorbidities evolution, and immunosuppressor modification after BS. Weight loss was reported as body mass index (BMI) and excess weight loss rate (%EWL) according to the formula:

$$(\text{preoperative weight} - \text{weight at follow-up}) / (\text{preoperative weight} - \text{ideal weight}).$$

Ideal weight was set at BMI=25 kg/m^2.

Data are presented according to the timing of BS and LT, before, during, and after.

Statistical Analysis

The methodological limitations, the incomplete reporting of data prohibited the use of meta-analyses. Mortality and morbidity were reported as relative rates, and a generalized linear mixed model framework with an underlying Poisson distribution was performed to compare different groups. Concerning the change in BMI, and %EWL, patient data were summarized using descriptive statistics and expressed as weighted means. Because of the low number of patients in each group, hypotheses were not tested and thus inferential statistics were not required. This review is predominantly qualitative descriptive due to the heterogeneous nature of the included studies.

Results

Study Selection

The attrition diagram outlining the screening process is depicted in Fig. 1. The initial search resulted in 311 studies. Seven studies reporting LT after BS were excluded as reporting hepatic failure secondary to a bariatric procedure

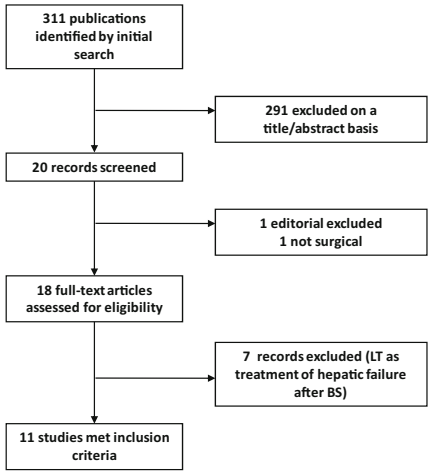

Fig. 1 Attrition diagram. *LT* liver transplantation, *BS* bariatric surgery

[13–19]. The exhaustive list of publications is available in the "Appendix." After selection, 11 papers were included for analysis.

Study Characteristics

The characteristics of the included articles are shown in Table 1. Most of these studies were case reports (6/11) and were mainly conducted in the USA [20–26], with one study each from Italy [27] and Chili [28]. The five remaining studies, accounting for 49/56 patients, reported 26 bariatric procedures before LT [20, 21], 7 concomitant with LT [23], and 16 after LT [26, 29].

The Quality of the Included Studies

More than half of the retrieved studies (6 out of 11) were case reports, while the others were single-center series reporting up to 20 patients. Outcomes such as mortality and postoperative morbidity were reported in all studies; nevertheless, weight loss was irregularly reported and in a few cases (when possible), we calculated the percentage of excess weight loss. The evolution of comorbidities, modification of immunosuppression, and quality of liver function were not sufficiently reported to allow a relevant analysis.

Patient Characteristics

Patients were divided into three groups according to the timing of BS and LT: BS before LT, during LT, and after LT (Table 2).

Table 1 Selected studies

Author (reference)	Year	Country	No. pts
BS before LT			
Takata et al. [20]	2008	USA	6
Lin et al. [21]	2013	USA	20
BS during LT			
Campsen et al. [22]	2008	USA	1
Heimbach et al. [23]	2013	USA	7
BS after LT			
Duchini et al. [30]	2001	USA	2
Tichansky et al. [24]	2005	USA	1
Butte et al. [28]	2007	Chili	1
Gentileschi et al. [27]	2009	Italy	1
Elli et al. [25]	2012	USA	1
Lin et al. [29]	2012	USA	9
Al-Nowayalati et al. [26]	2013	USA	7
Total	2001–2013	9 USA 1 Chili 1 Italy	56

Surgical characteristics are available in Table 3. Sleeve gastrectomy (SG) was the most common procedure regardless of the timing of BS (44/56). Roux-en-Y gastric bypass (RYGB) was done in 10 patients (17.9 %), gastric banding and bilio-pancreatic diversion (BPD) on 1 patient each (1.8 %). Two patients had an intragastric balloon (BIB) before BPD and sleeve gastrectomy, respectively. In the first case, BIB+BPD were performed after LT, while in the second case, BIB was positioned prior to LT and SG was realized after.

A laparoscopic approach accounted for 35 operations (62.5 %) versus 20 open (35.7 %). One procedure was performed under robotic assistance (1.8 %).

The mean BMI at BS for all the patients was 46.8±3.8 kg/m^2, and the sex distribution was almost equal (M 17, F 19).

The main indications for LT were hepatitis C virus (HCV) in 35 % (11/31) of patients and NASH in 32 % (10/31). Other indications for LT were alcoholic hepatitis (3/31, 10 %), hepatitis B virus, hereditary hemorrhagic telangiectasia, autoimmune hepatitis, alpha 1-antitrypsin deficiency, hemangioendothelioma, and jejuno-ileal bypass.

Mortality and Morbidity

No death was reported in the early postoperative course (<30 days). Six patients died during follow-up: three transplanted patients died in the first postoperative year after BPD (n=1) and gastric bypass (n=2) and another 3 died after sleeve gastrectomy on the waitlist before LT. No postoperative complications were reported in the six case reports. In the four studies reporting more than two cases, 12 % (5/42) of patients required at least one surgical reintervention for complications after the bariatric procedure (Table 4.) No statistical difference was found in mortality or morbidity incidence rate.

Weight Loss

Weight loss was reported either as percentage excess weight loss (%EWL) or as BMI (Table 5). At 1 year of follow-up, %EWL was 53.9 % and mean BMI had decreased from 46.8 to 33.5 kg/m^2 (excess BMI loss 46.5 %).

Liver Function and Immunosuppression

In five studies, the authors declared that the liver function of the graft improved after BS, but only two reported laboratory findings before and after BS. Postoperative liver biopsy was available in one study [30] and reported a reduced liver steatosis, an absence of fibrosis and minimal portal inflammation. Immunosuppressive drugs were reported as stable in

Table 2 Patients' characteristics

Authors	No. pts	Sex (M/F)	Type of cirrhosis	Child	MELD	Age at BS	Age at LT	BS/LT interval (years)	BMI at BS	BMI at LT
BS before LT										
Takata et al.[20]	6	2/4	1 HCV+HBV, 2 NASH, 2 HCV+ETOH,1 AH	4 Child A 2 Child B	NS	52.3	NS	NS	49.3±6.4	NS
Lin et al. [21]	20	17/9[a]	NS	NS	11	57[a]	56[a]	1.4	48.3±5.4[a]	32.9[b]
Total	26	N/A	3HCV, 2 NASH			55.9	56[a]	1.4	48.5	32.9
BS during LT										
Campsen et al. [22]	1	0/1	1 AH	NS	NS	28	28	0	42	42
Heimbach et al. [23]	7	4/3	4 NASH, 1 HHT, 1 NASH+HCV, 1 Alpha-1	NS	32	53	53	0	48±4.5	48±4.5
Total	8	4/4	5 NASH, 4 others			49.9±10.2	49.9±10.2	0	47.3±4.7	47.3±4.7
BS after LT										
Duchini et al. [30]	2	1/1	1 NASH, 1 NASH+HCV	NS	NS	37.7	35.5	2.2	52.5	49.7
Tichansky et al. [24]	1	1/0	HCV	NS	NS	49	47	2	54	NS
Butte et al. [28]	1	1/0	NASH	NS	NS	61.8	61	0.8	37.9	41.3
Gentileschi et al. [27]	1	1/0	HCV	NS	NS	57	46	11	53.6	30.9
Elli et al. [25]	1	0/1	HCC+HCV	NS	NS	NS	62	NS	53	41
Lin et al. [29]	9	3/6	NS	NS	NS	56.8	51.9	5.9	40.6±3.3	28.9±7.5
Al-Nowayalati et al. [26]	7	4/3	4 HCV, 1 ETOH, 1 HET, 1 JIB	NS	NS	55.4	53.2	2.2	44.3±6.1	34.3±5.5
Total	22	11/11	7 HCV, 3 NASH, 4 others			54.7	51.2	3.9	44.5	32.4
Total all timing	56	17/19	11 HCV, 10 NASH, 9 others			54.6	50.9		46.8	36.4

NS not stated, *N/A* not applicable, *BS* bariatric Surgery, *LT* liver transplantation, *HCC* Hepatocellular carcinoma, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *ETOH* alcoholic hepatitis, *Alpha-1* alpha 1-antitrypsin deficiency, *AH* autoimmune hepatitis, *HHT* hereditary hemorrhagic telangiectasia, *HET* hemangioendothelioma, *JIB* jejuno-ileal bypass, *BIB* intragastric balloon, *BPD* biliopancreatic diversion

[a] Including 6 patients with end-stage renal disease

[b] BMI for 6/20 patients that received LT after BS

five studies, but pre and postoperative dosage and serum levels were available in only two studies [29, 30].

Discussion

Very few data are currently available on the surgical treatment of morbid obesity in patients in the setting of LT. Most of the retrieved studies are case series reporting one or two cases and only one study reports more than 10 cases [21].

BS seems to be feasible and effective in this population regardless of the timing or the type of surgery. With losses of excess weight of 53.9 and 66 % at 1 and 2 years of mean follow-up, respectively, the effectiveness of BS in this particular population is comparable to what is reported in the general population undergoing BS [31–34].

No death was reported in the early postoperative period (<30 days). However, six patients (10.7 %) died during follow-up, with three dying within the first 9 months after BS. The total reoperation rate was 12.2 % (6/49) and in the 22 sleeve gastrectomies (SG), there were two staple-line leaks (9 %), almost twice as many as reported in the general population [35].

Considering the type of patients, we consider the mortality and morbidity rates are acceptable; nevertheless, they should be interpreted with caution because of the heterogeneity in the bariatric procedures employed, the incompleteness of the data, and the presence of case reports that may represent a selection bias.

Table 3 Surgical details

Author	No. pts	Surgical procedure	Approach	Bariatric Surgery		Liver transplantation	
				OT (min)	LOS (days)	OT (min)	LOS (days)
BS before LT							
Takata et al. [20]	6	SG	Lap	141	4,2	N/A	N/A
Lin et al. [21]	20	SG	Lap	151±58.6	4.2±1.2	NS	NS
Total	26	26 SG	26 Lap	149	4.2		
BS during LT							
Campsen et al. [22]	1	AGB	Open	30[a]	8	333	8
Heimbach et al. [23]	7	SG	Open	38[a]	28.9±46.1	299±73.3	28.9±46.1
Total	8	1 AGB, 7 SG	8 open	37	26.3	303	26.3
BS after LT							
Duchini et al. [30]	2	RYGB	Open	NS	NS	NS	NS
Tichansky et al. [24]	1	RYGB	Lap	NS	3	NS	NS
Butte et al. [28]	1	SG	Open	NS	6	NS	NS
Gentileschi et al. [27]	1	BPD	Open	NS	N/A	NS	NS
Elli et al. [25]	1	SG	Robotic	158	4	NS	NS
Lin et al. [29]	9	SG	Lap (8), open (1)	165±68	5.3±3.8	NS	NS
Al-Nowayalati et al. [26]	7	RYGB	Open	NS	NS	NS	NS
Total	22	11 SG, 10 RYGB, 1 BPD	12 open, 12 Lap, 1 robotic	164	5.1		
Total all timing	56	44 SG, 10 RYGB, 1 AGB, 1 BPD	35 Lap, 20 open, 1 robotic	126	8.2		

NS not stated, *N/A* not applicable, *SG* sleeve gastrectomy, *AGB* adjustable gastric banding, *RYGB* Roux-en-Y gastric bypass, *BPD* biliopancreatic diversion, *Lap* laparoscopic

[a] Estimated time for bariatric procedure during LT

Techniques

Concerning the type of bariatric procedure, the whole panel of current techniques is present (gastric banding, sleeve gastrectomy Roux-en-Y gastric bypass, and biliopancreatic diversion), although SG is the most common (44/56). Authors [21, 23, 25, 28] justified this choice by explaining that this technique has been preferred because it does not modify the endoscopic access to the biliary tract and, theoretically, does not include any intestinal bypass; thus, it does not affect the absorption of immunosuppressive medications. Nevertheless, in the retrieved studies in this review, no rigorous pharmacokinetics evaluation has been done on immunosuppression drugs. Authors generally report that the dose and serum levels of immunosuppressors remain stable [25, 27–30]. More information about pharmacokinetics after BS is available for kidney transplantation. A few studies report that transplant recipients with gastric bypass need higher doses of tacrolimus, sirolimus, MMF, and cyclosporine [36, 37] and this procedure is reported as safe and effective in this type of patient.

Endoscopic access to the biliary tree after gastric bypass remains a real issue. Biliary complications are not infrequent after LT, as they have been reported in up to 17 % of patients after deceased donor LT [38]. Bile leaks usually occur in the early postoperative period, while strictures can occur even several years later. A Dutch study [39] reported a cumulative risk of anastomotic strictures of 6.6, 10.6, and 12.3 % at 1, 5, and 10 years after LT, respectively. However, this may not be a true limitation as biliary complications can be managed by interventional radiology by the transhepatic route or by surgery [40]. Only one paper reported about gastric banding. This was quite surprising as this procedure has the lowest postoperative complication rate, does not modify the digestive tract, does not cause malabsorption, and does not imply anastomosis or gastric resection. However, long-term band results are controversial: even though a recent review reported good weight loss up to 15 years [32], several studies on national trends show a progressive reduction in the use of gastric banding [41–45].

Timing

All possibilities have been explored regarding the timing of BS and LT.

Table 4 Mortality and morbidity of bariatric surgery

Author	No. pts	Follow-up	Mortality		BS complications		Reoperation	
		Mean (range)	No. (delay)	Incidence rate (CI)	No.	Incidence rate (CI)	No. (%)	Incidence rate (CI)
BS before LT								
Takata et al. [20]	6	9 (3–19)	0	0 (0–6.8)	2	3.7 (0.4–13.4)	1 (16.7 %)	1.9 (0–10.3)
Lin et al. [21]	20	NS (6–48)	3 (4y, NS, NS)	2.5 (0.5–7.3)	3	2.5 (0.5–7.3)	1 (5.0 %)	0.8 (0–4.6)
Total	26	N/A (6–48)	3/26 (11.5 %)		5/26 (19.2 %)		2/26 (7.7 %)	
BS during LT								
Campsen et al. [22]	1	6	0	0 (0–61.5)	0	0 (0–61.5)	0	0 (0–61.5)
Heimbach et al. [23]	7	17 (8–33)	0	0 (0–3.1)	1	0.8 (4.7)	1 (14.3 %)	0.8 (4.7)
Total	8	15.6 (6–33)	0		1/8 (12.5 %)		1/8 (12.5 %)	
BS after LT								
Duchini et al. [30]	2	27 (18–36)	0	0 (0–6.8)	0	0 (0–6.8)	0	0 (0–6.8)
Tichansky et al. [24]	1	4	0	0 (0–92.2)	0	0 (0–92.2)	0	0 (0–92.2)
Butte et al. [28]	1	6	0	0 (0–61.5)	0	0 (0–61.5)	0	0 (0–61.5)
Gentileschi et al. [27]	1	9	1 (9 months)	11.1 (0.3–61.9)	0	0 (0–41)	0	0 (0–41)
Elli et al. [25]	1	3	0	0 (0–123)	0	0 (0–123)	0	0 (0–123)
Lin et al. [29]	9	5 (3–12)	0	0 (0–8.2)	3	6.7 (1.4–19.5)	3 (33.3 %)	6.7 (1.4–19.5)
Al-Nowayalati et al. [26]	7	59 (6–103)	2 (6 months, 9 months)	0.5 (0.1–1.7)	4	1 (0.3–2.5)	NS	N/A
Total	22	24.2 (3–103)	3/22 (13.6 %)		7/22 (31.8 %)		3/15 (20 %)	
Total all timing	56		6/56 (10.7 %)		13/56 (23.2 %)		6/49 (12.2 %)	

NS not stated, *N/A* not applicable, *BS* bariatric Surgery, *CI* confidence Interval

Table 5 Weight loss after bariatric surgery

Author	No. pts	BMI (no.)						%EWL (no.)				
		At surgery	3 months	6 months	12 months	24 months	≥36 months	3 months	6 months	12 months	24 months	≥36 months
BS before LT												
Takata et al. [20]	6	49.3										
Lin et al. [21]	20	48.3[a]	40 (20)	37.6 (20)	34.1 (18)	29.4 (11)		26 (20)		50 (18)	66 (11)	
BS during LT												
Campsen et al. [22]	1	42.0		34 (1)					45 (1)			
Heimbach et al. [23]	7	48.0			28 (1)	34 (1)	23 (1)					
BS after LT												
Duchini et al. [30]	2	52.5	43.2 (2)	36.6 (1)	29.1 (1)		38.8 (1)	52.8 (2)	69.8 (1)	89.3 (1)		64.7 (1)
Tichansky et al. [24]	1	54.0	43 (1)									
Butte et al. [28]	1	37.9		29.8 (1)					63 (1)			
Elli et al. [27]	1	53.0	48 (1)									
Lin et al. [25]	9	40.6						38.1 (9)	55.5 (4)	65.4 (3)		
Gentileschi et al. [29]	1	53.6		42 (1)					41 (1)			
Al-Nowayalati et al. [26]	7	44.3		32.5 (1)			25.7 (5)					
Weighted mean	56	46.8	40.7 (24)	37.1 (25)	33.5 (20)	29.8 (12)	27.2 (7)	31.2 (31)	55.1 (8)	53.9 (22)	66 (11)	64.7 *n*

BS bariatric surgery, *LT* liver transplantation, *BMI* body mass index, *%EWL* percentage of excess weight loss

[a] Including 6 patients with end stage renal disease

Surgical treatment of obesity in the first place aims to improve the accessibility to and the outcome of LT. Although several studies have reported good results of transplantation in obese recipients [46], obesity still remains a contraindication for the American Association for the Study of Liver Diseases and obese patients suffer from a limited access to LT [47]. It seems logical to reduce weight in transplant candidates, but this approach has some limitations as operating on transplant candidates comes down to operating on cirrhotic patients.

A few studies have been published on cirrhosis and BS [48–51]. In most of those cases, cirrhosis was unknown before the bariatric procedure and when the Child-Pugh classification was used, almost all patients were Child A. Complications rated up to 34.8 % have been reported, with a leak rate of up to 12.5 % [48]. Mortality was also higher than in the general population [52, 53]. In single-center studies, one death occurred in the early postoperative time out of 61 patients [48–50]. Nevertheless, in a national survey, surgeons responding to the questionnaire reported a mortality rate for cirrhotic patients after BS of 4 % [50]. Similarly, a register study, based on the National Income Sample, reported a 1.2 % mortality for this specific population [51].

In the two studies on BS before LT retrieved for our review [20, 21], mortality was nil and reoperation rates were 5 and 16.6 %. There are two limitations to the "bariatric first" approach: the prevalence of obesity in transplant candidates is generally reported to be lower than in the general population [54] and one third of transplant recipients develop a de novo obesity and metabolic syndrome in the years following LT. For all these reasons, though BS prior to LT probably improves the outcome of LT, its real impact on the natural history of obesity (and its comorbidities) in liver recipients seems to be limited.

BS concomitant to LT could be an interesting option, as it would reduce the number of major surgeries. Nevertheless, only two studies have been reported and information is limited.

Gastric banding and sleeve gastrectomy seem to be feasible and effective for weight loss in strictly selected patients. Nevertheless, complication rates are 3 to 4 times higher than in the general population, with a staple line leak rate of 14.3 % (1/7) and a reoperation rate of 12.5 % (1/8). The important early immunosuppressive therapy and the nutritional status of these patients could explain the high morbidity rate. Furthermore, this simultaneous approach requires the logistic availability of a hepatic and a bariatric surgeon. Again, all these constraints considerably limit the use of this approach.

The third possibility is BS after LT. The clear advantage of this approach is the selection of patients surviving LT and developing (or maintaining) obesity in the following years. Intervention is reported as technically challenging and has been performed directly by an open approach in almost half of patients (10/22). Again, morbidity is higher than in the general population: a reoperation rate of 33 % (3/9) was reported by Lin. Notably, though no postoperative death has been reported, three patients died in the first postoperative year after BS (13.6 %).

With such a high morbidity rate of BS in the setting of LT, very little has been published on minimally endoscopic techniques of obesity surgery. We found only three cases of intragastric balloon (BIB) in the literature. The first was reported in the study of Gentileschi [27], included in this review, as a first step before BPD [27]. BIB was performed after LT, and allowed an excess weight loss of 28 kg in 6 months (EWL 20 %). In the second case, also included in this review [28], BIB was performed in a patient on the waitlist for LT with a BMI of 47 kg/m^2. The patient lost 18 kg with a reduction of almost 6 points of BMI (41.3 kg/m^2). LT took place more than 2 years later and was complicated by a biliary stenosis. As endoscopic treatment happened to be unsatisfactory, a surgical repair was planned, and a Roux-en-Y biliary diversion was performed at the same time. The final case was reported by Choundary [55]. The balloon was positioned prior to LT. Weight loss was consistent: BMI reduced by 9.2 kg/m^2, equivalent to an EWL of 39.1 %. No complications were reported in these two cases.

The main limitation of the present review is the limited number of studies eligible for analysis. Furthermore, patients undergoing BS before, during, or after LT constitute three heterogeneous populations of patients, rendering comparisons difficult. In the first case, patients suffer from their original liver pathology and are often malnourished. In the second situation (BS concomitant to LT), patients undergo two major surgeries while still in a poor nutritional status and receive an intensive immunosuppression therapy, yet have a new functional liver. Patients undergoing BS years after LT have lower doses of immunosuppressing drugs and are usually in a better nutritional status. However, data on liver function and immunosuppression therapy after BS are still lacking. Finally, case reports were included in the present review because of the poverty of the available data, although case reports are an additional source of bias in term of surgical results.

Conclusion

In conclusion, BS is feasible and effective in patients before, during, and after LT. Morbidity and mortality are higher than

in the general population undergoing BS, but remain acceptable. Rigorous follow-up of hepatic function evolution and the pharmacokinetics of immunosuppressors should be done to better understand the natural history of these patients.

Less invasive procedures, such as BIB, may find a place in the treatment of obesity in this very particular population of patients.

Conflict of Interest Andrea Lazzati declares no conflict of interest. Antonio Iannelli declares no conflict of interest. Anne-Sophie Schneck declares no conflict of interest. Anaïs Charles Nelson declares no conflict of interest. Sandrine Katsahian declares no conflict of interest. Jean Gugenheim declares no conflict of interest. Daniel Azoulay declares no conflict of interest.

As this study is a meta-analysis conducted on articles previously published, no informed consent is required.

For this type of study, formal consent is not required

Appendix

Table 6 Screened records

	Author	Year	Decision	Reason
1	Burke	1992	Excluded	LT as treatment of hepatic failure after BS
2	D'Souza-Gburek	1997	Excluded	LT as treatment of hepatic failure after BS
3	Lowell	1997	Excluded	LT as treatment of hepatic failure after BS
4	Markowitz	1998	Excluded	LT as treatment of hepatic failure after BS
5	Duchini	2001	Included	
6	Castillo	2001	Excluded	LT as treatment of hepatic failure after BS
7	Tichansky	2005	Included	
8	Butte	2007	Included	
9	Takata	2008	Included	
10	Campsen	2008	Included	
11	D'Albuquerque	2008	Excluded	LT as treatment of hepatic failure after BS
12	Mandel	2008	Excluded	Editorial
13	Gentileschi	2009	Included	
14	Elli	2012	Included	
15	Lin	2012	Included	
16	Heimbach	2013	Included	
17	Lin	2013	Included	
18	Al-Nowayalati	2013	Included	
19	Choundary	2013	Excluded	Not surgical
20	Auclair	2013	Excluded	LT as treatment of hepatic failure after BS

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A simple model to predict moderate to severe steatosis in morbidly obese liver donors.

Original Article

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Running title: A model to predict steatosis in obese donors

Key words: obesity, macrovesicular steatosis, liver harvesting, liver transplantation, statistical model

Abstract

Background: In the selection of marginal liver grafts most transplantation centers use a cut-off of 30% macrovesicular steatosis to define an acceptable risk of non-function. The quantification of steatosis still relies on macroscopic evaluation by the harvesting surgeon with the aid of a parenchymal biopsy, when available. The aim of this study was to create a non-invasive model to predict >30% steatosis based on simple clinical and biochemical markers available at the time of potential liver-donor evaluation, to avoid futile and expensive procurement proceedings.

Methods: Data from 857 morbidly obese patients, operated on for bariatric surgery in our center, were prospectively collected. Liver biopsies were obtained and patients were divided into two groups according to the degree of steatosis, classified as absent to mild (0–30%) and moderate to severe (>30%). Univariate and multivariate analysis were performed to identify parameters associated with steatosis of >30%.

Results: Steatosis of >30% was found in 55% of the study population. Age, alanine aminotransferase (ALT), and waist circumference were found to be independently associated with steatosis of >30%. By combining these parameters, we developed a model to predict steatosis of >30% with an area-under-the-receiver-operating characteristic (AUROC) of 0.78 (95% CI: 0.75–0.81). The best threshold was 0.06, which offered a sensitivity of 72% and a specificity of 70%.

Conclusions: A model that combines three simple biological parameters can accurately predict steatosis of >30% in morbidly obese patients, and could improve the selection of marginal grafts before activating procurement proceedings.

Introduction

The growing discrepancy between the availability of donor organs and the need for liver transplantation has led many centers to expand criteria for acceptance of marginal grafts, particularly steatotic grafts (1). A significant correlation exists between the risk of graft failure and the percentage of macrovesicular steatosis (2-5). The cut-off value of 30% steatosis is used by most centers to accept or reject a liver graft. Indeed the use of a graft with mild steatosis (<30%) has similar results to transplantation with a non-fatty graft, while moderate to severe steatosis (>30%) exerts a clear impact on graft function and results in a high rate of organ failure (6-8).

Liver steatosis is part of non-alcoholic fatty liver disease (NAFLD), which encompasses a spectrum of liver diseases associated with insulin resistance and visceral obesity (9), and has a prevalence of 67–75% among obese subjects (10-12). As the number of obese donors has increased (proportionally with the epidemic of obesity), a considerable number of obese donors' grafts are likely to be steatotic. Data from the American Organ Procurement and Transplantation Network (OPTN) show that, in 2013, 30% of deceased liver donors were obese (body-mass index [BMI] >30 kg/m^2) and 5% presented with a BMI >40 kg/m^2 (13). However, the BMI, currently used to define obesity, correlates weakly with the presence and severity of steatosis (14-18).

At present, no clinical or biochemical marker can estimate the degree of fatty infiltration of the liver. In addition, the decision to activate a harvesting team depends on rapid assessment of the potential liver donor based on a few clinical and biological parameters, and liver ultrasonography (US), to give a crude estimation of steatosis (19). Therefore, in most cases, the final decision regarding the acceptance of a marginal liver graft is taken by the harvesting surgeon, who evaluates the macroscopic appearance of the organ and may eventually perform a parenchymal biopsy, which is not always available for logistic reasons, but remains the gold standard for diagnosing and staging steatosis. However, this attitude requires direct access to the cadaveric liver, which mandates the harvesting team being activated, a pathologist called-in, and a great amount of human and economic resources being mobilized.

The aim of this study was to define a score to predict the presence of >30% steatosis in morbidly obese donors, based on simple clinical and biochemical markers that are available at the time when a potential liver donor is evaluated, to avoid futile procurement proceedings.

Materials and methods

Study design

The study was performed according to French legislation regarding Ethics and Human Research, and was approved by the local Ethics Committee (Huriet-Serusclat law, DGS 2003/0395). Written informed consent was obtained from all patients. All patients met the 1991 National Institutes of Health (NIH) Consensus Conference guidelines for bariatric surgery (20). Data were collected prospectively and entered into a database.

This prospective database of morbidly obese patients undergoing bariatric surgery at a single center was used to build a model predictive of the presence of liver steatosis of >30%. The parameters collected in the database were simple clinical and biochemical markers that are available in the medical record provided by the French agency for organ procurement and transplantation (Agence de la Biomédecine), for any potential liver donor. In order to consider the metabolic disturbances that play a central role in the pathophysiology of NAFLD, we included only qualitative parameters in our analysis, i.e., history of type-2 diabetes mellitus (T2DM), high triglycerides, high cholesterol, and high blood pressure. Since our cohort was not composed of cadaveric donors, we decided to exclude quantitative parameters that can be widely influenced by the particular hormonal and hemodynamic situation of brain death, i.e. plasma glucose, insulin, triglycerides, cholesterol, blood pressure …

Patient selection and preoperative workup

All patients were negative for hepatitis B and C viral markers, auto-antibodies indicative of autoimmune hepatitis, and had negligible alcohol consumption (<20 g/day in women and <30g/day in men). Alcohol abuse was also excluded by interviewing the patients' relatives. Preoperative workup included blood-pressure determination and anthropometric measurements: weight, height, waist circumference (WC). Blood samples, obtained before surgery and after overnight fasting, were used to determine plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and total bilirubin. In our center the upper limits of normal AST and ALT for women are 31 and 40 IU/L, while for men they are 37 and 41 IU/L, respectively. The upper limit of normal GGT is 32 IU/L for females and 41 IU/L for males, respectively.

T2DM was defined by two elevated measurements for fasting plasma glucose ≥7 mmol/L. High triglyceride was a triglycerides level of ≥1.7 mmol/L (or treatment for hypertriglyceridemia). High cholesterol was defined as HDL-cholesterol of <1.29 mmol/L in women and <1.03 mmol/L in men. High blood pressure was defined as systolic blood pressure (BP) ≥130 mmHg or diastolic BP ≥85 mmHg or the use of medications to treat high blood pressure.

Metabolic syndrome (MS) was diagnosed according to the definition by Alberti et al (21), which consists of the presence of three of the following five parameters: (1) central obesity, defined as a WC ≥80 cm in females and ≥94 cm in males; (2) TG ≥1.7 mmol/L or treatment for this; (3) HDL-cholesterol <1.30 mmol/L in women and <1 mmol/L in men; (4) systolic blood pressure ≥130 mm Hg, or diastolic blood pressure ≥85 mm Hg, or treatment for hypertension; and (5) fasting plasma glucose ≥5.6 mmol/L or previously diagnosed T2DM. All the morbidly obese patients in this study had an increased WC.

Pathological liver assessment

A hepatic wedge biopsy was obtained during bariatric surgery by surgeons specialized in liver surgery and transplantation (AI and JG). Hepatic wedges were at least 10 mm long. Specimens were reviewed by one liver pathologist (SP) without knowledge of the clinical or biological characteristics of the patients. Routine hematoxylin–eosin–safran and sirius red staining was performed on all biopsies. The diagnosis was retained according to the modified Brunt criteria for diagnosis of NAFLD (22). We defined macrovesicular steatosis as hepatocytes that contained one large vacuole of fat displacing the nucleus peripherally: this was graded as absent to mild (0–30%) or moderate to severe (>30%) based on the percentage of cells containing cytoplasmic fat droplets.

Statistics

Quantitative variables are presented as their means ± standard deviations. Quantitative values were compared between patients with steatosis ≤30% and >30% using the Mann–Whitney test or Student's *t*-test, as appropriate. The chi-squared test was used to compare qualitative values. Logistic regression analyses were performed to determine the independent parameters associated with steatosis of >30%. Parameters assessed in the logistic regression included significant and relevant ones avoiding redundancy (components of the MS were introduced into the logistic regression separately, but not the MS itself; similarly, ALT but not AST was included). Using the independent parameters obtained from the logistic regression, models were constructed using another logistic regression restricted to the significant parameters. Using a receiver-operating-characteristic (ROC) curve and area-under-the-ROC (AUROC) curve analysis we evaluated the diagnostic accuracy of the final model to predict steatosis of >30% (23).

A significance level of p <0.05 was used in all analyses. All calculations were made using NCSS 2007 software (Saugus MA 01906, U.S.A.).

Results

Characteristics of the study population

A total of 857 patients undergoing bariatric surgery in our center were enrolled in this study between January 2003 and June 2013.

Baseline characteristics of the study population are shown in Table 1. Patients were mainly middle-aged women with a mean BMI of 43.5 ± 5.2 kg/m^2. In the entire cohort, the prevalence of T2DM, high triglycerides, high cholesterol, high blood pressure, and MS were 15.5%, 10.5%, 15.6%, 31.4%, and 37.3%, respectively. Liver biopsies showed that steatosis of >30% was present in 471 patients, corresponding to 55% of the study population.

Variables predicting liver steatosis of >30%

Patients were divided into two groups according to the severity of liver steatosis (≤30% vs. >30%) and a comparison was made between these two groups to find which parameters were associated with a steatosis of >30% (Table 1).

A significantly higher prevalence of T2DM, high triglycerides, high cholesterol, high blood pressure, and MS was found in the group with steatosis of >30%. Similarly, patients with moderate to severe steatosis presented with significantly higher levels of the biological parameters that reflected liver injury (i.e., higher levels of ALT, AST and GGT, but not bilirubin). Age and male gender were also significantly associated with steatosis of >30%.

Multivariate analysis showed that age, WC, ALT, and a history of T2DM were independently associated with steatosis of >30% (Table 2).

A model to predict the presence of steatosis of >30%

Logistic regression was conducted to predict steatosis of >30% by combining the four parameters that were significant in the multivariate analysis (age, ALT, WC, T2DM) (Table 3). As the history of T2DM was not significantly predictive of the presence of steatosis of >30%, a second model was conducted that combined three parameters (age, WC, ALT) (Table 4) The model's R^2 was 0.18. This model was based on the following logistic regression equation:

-6.17367949123914 + 2.38344957580222E-02*age (years) + 5.42653776114211E-02*ALT (IU/L) + 3.15944824899485E-02*WC (cm).

A ROC curve was constructed to assess the diagnostic accuracy of this model (Figure 1). The AUROC was 0.78 (range: 0.75–0.81). The best threshold of this model was 0.06, which offered a sensitivity of 72.3 % and a specificity of 70%, a positive predictive value of 75.8% and a negative predictive value of 21.1%.

Discussion

In the present study, we have shown that age, WC, and ALT were independently predictive of liver steatosis of >30% in a prospective cohort of morbidly obese patients undergoing bariatric surgery. The combination of these three simple parameters resulted in an equation that could predict steatosis of >30%, with a sensitivity of 72.3%, a specificity of 70%, and an AUROC of 0.78.

Macrosteatosis of liver grafts increases the susceptibility to ischemia-reperfusion injury and is, therefore, closely related to the functional recovery of the graft after transplantation (24). The cut-off value for macrosteatosis of 30% is accepted by most transplantation centers for graft acceptance (6-8). Such a crucial element is currently evaluated by the harvesting surgeon during organ procurement on the base of the results from a frozen biopsy, when available, or even solely by macroscopic assessment of the organ. If the graft is rejected, a large amount of economical and human resources have been wasted. However, with the recent epidemic of obesity and the shortage of organs, potential donors cannot be rejected on the basis of the presence of obesity defined by the BMI only. Indeed, about half of the patients in the present study had steatosis of <30% and, thus, could have provided a suitable graft for liver transplantation.

An ideal method to predict liver-graft steatosis should be able to predict, with high accuracy, steatosis of >30%, the procedure should be simple, and be based on clinical and biochemical parameters that are readily available at the time of cadaveric-donor announcement.

Magnetic-resonance spectroscopy (MRS) is the best imaging modality to grade the severity of steatosis with high accuracy (25, 26), but it is not broadly available and its routine application is not perceived practical in the pre-transplant setting. On the other hand, US is cheap and easily available, and provides good accuracy for the diagnosis of hepatic steatosis, but it is operator dependent with low inter- and intra-observer agreement on the severity of steatosis (16, 19).

Clinical and biochemical markers have been incorporated into several diagnostic panels, which have been proposed in the literature to predict steatosis in a variety of populations of patients (16). The Steatotest, which incorporates 12 variables, showed reasonable accuracy, with a 0.79 AUROC for moderate–severe steatosis, when tested in a French cohort of more than 700 patients (27). However, the main limits of this test are the small positive predictive value at 63% and the use of parameters not routinely available. The NAFLD Liver Fat Score, derived from a Finnish population, yielded 86% sensibility and 71% specificity for NAFLD identification using MRS as the gold standard (28).

When we limit research to liver donors, the literature about non-invasive methods for predicting steatosis is scanty. In a Korean study on 589 potential living-liver donors, Lee et al. showed that being aged >30 years, obesity, and hypertriglyceridemia were significant risk factors for steatosis of >30% (29). The authors did not include ALT into their multivariate analysis, but found that the number of donors with elevated ALT increased significantly as the severity of steatosis increased from mild to severe. In a study of 374 deceased liver donors, Cucchetti et al. created a model that combined five risk factors that were independently correlated with the presence of moderate to severe steatosis: i.e., a higher BMI, elevated ALT, T2DM, a history of heavy alcohol consumption, US signs of fatty liver. This model accurately identified steatosis of >30%, with an AUROC of 0.86 (30). In the presence of none or one of the risk factors, liver steatosis will certainly be minimal, whereas in the presence of five risk factors, the chances of steatosis being <30% are virtually absent. Intermediate scores are less efficient at distinguishing moderate from severe steatosis. The main limitations of this study are its retrospective nature and the selection bias linked to the fact that only 374 of the 905 deceased liver donors were included in the analysis where a liver biopsy had been performed.

The strengths of our study rely on its prospective character, the simplicity of the model, the number of patients enrolled and the exhaustive work-up that included a liver biopsy: our study represents one of the largest series of bariatric-surgery patients reported in the literature. The major limitation is represented by the study population including only morbidly obese patients that have a higher risk of liver steatosis compared to the average population of potential deceased donors. In our cohort, a percentage as high as 55% presented with moderate to severe steatosis, which is in line with several previously reported bariatric surgery series (10-12). However, the model we report is an interesting tool to predict the presence of liver steatosis >30% in morbidly obese donors. The extrapolation of these results to non-obese donors should be done with care and a prospective validation of this model in the pre-transplant setting should be obtained to confirm its applicability in clinical practice.

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List of abbreviations used in the article

ALT: alanine aminotransferase

AST: aspartate aminotransferase

AUROC: area under the receiver operating characteristic

BMI: body mass index

GGT: gamma glutamyl transpeptidase

HDL: high-density lipoprotein

LDL: low-density lipoprotein

MS: metabolic syndrome

NAFLD: non-alcoholic fatty liver disease

NIH: National Institutes of Health

OPTN: Organ Procurement and Transplantation Network

ROC: receiver operating characteristic

T2DM: type-2 diabetes mellitus

TG: triglycerides

US: ultrasonography

WC: waist circumference

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Conflict of Interest Disclosure Statement

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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Fig. 1. Receiver-operating characteristic (ROC) curve of the model combining 3 parameters (age, waist circumference, alanine aminotranferase) to predict steatosis of >30% in morbidly obese patients.

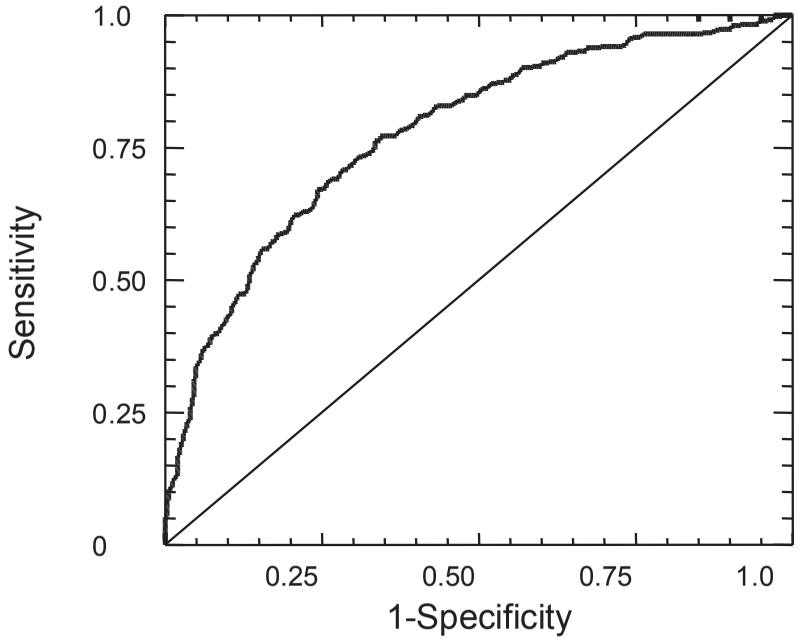

Table 1. Characteristics of the study population according to the severity of liver steatosis.

Variables	Whole population (n =857)	Steatosis ≤30% (n =386)	Steatosis >30% (n =471)	*P*
Age (years)	40.0 ± 11.7	37.8 ± 11.5	41.6 ± 11.6	0.001
Gender (M/F)	135/722	32/340	103/382	0.001
Height (cm)	164.5 ± 8.5	163.8 ± 7.7	165.0 ± 9.0	0.04
Weight (kg)	117.9 ± 18.4	115.6 ± 16.6	119.7 ± 19.5	0.001
BMI (kg/m^2)	43.5 ± 5.2	43.1 ± 5.1	43.8 ± 5.2	0.06
Waist circumference (cm)	120.6±14.3	116.6 ±13.8	123.6± 13.9	0.001
Type 2 diabetes (%)	15.5	9.5	20.5	0.001
High triglycerides (%)	10.5	6.8	14.0	0.001
High cholesterol (%)	15.6	12.0	18.9	0.001
High blood pressure (%)	31.4	19.8	32.6	0.001
Metabolic syndrome (%)	37.3	23.1	49	0.001
AST (IU/L)	28.5 ± 14.6	23.3 ± 7.2	32.6 ± 17.3	0.001
ALT (IU/L)	35.5 ± 26.0	24.7 ± 12.8	43.7 ± 30.2	0.001
GGT (IU/L)	42.2 ± 43.9	33.4 ± 43.2	48.9 ± 42.9	0.001
Total bilirubin (micromol/l)	7.4 ± 3.7	7.3 ± 3.3	7.5 ± 4.1	NS

Values are mean ± standard deviation unless stated otherwise

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase

Table 2. Multivariate analysis (logistic regression) of parameters associated with steatosis of >30% (r^2=0.19).

	OR	95% CI	P
Age	1.02	1.00-1.03	0.04
Gender (F)	1.13	0.61-2.09	0.7
Weight	0.99	0.98-1.004	0.16
Waist circumference	1.04	1.02-1.06	0.001
Type 2 diabetes	1.73	1,03-2.93	0.04
High triglycerides	1.61	0.87-2.98	0.13
High cholesterol	0.82	0.49-1.37	0.45
High blood pressure	1.004	0.66-1.52	0.99
ALT	1.06	1.05-1.07	0.001
GGT	0.99	0.99-1.00	0.19

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase; OR, odds ratio ; CI, confidence interval

Table 3. First model for the prediction of steatosis of >30%, R^2=0.18

	OR	95% CI	P
Age	1.02	1.005-1.03	0.009
ALT	1.05	1.04-1.07	0.001
Waist circumference	1.03	1.02-1.05	0.001
History of type 2 diabetes	1.5	0.9-2.46	0.1

ALT, alanine aminotransferase; OR, odds ratio ; CI, confidence interval

Table 4. Second model for the prediction of steatosis of >30%, R^2=0.18

	OR	95% CI	P
Age	1.02	1.01-1.04	0.001
ALT	1.06	1.04-1.07	0.001
Waist circumference	1.03	1.02-1.05	0.001

ALT, alanine aminotransferase; OR, odds ratio ; CI, confidence interval

NASH chez le patient obèse sévère

Une indication de la chirurgie bariatrique

Dr Anne-Sophie Schneck*, Dr Rodolphe Anty*, Pr Jean Gugenheim*, Pr Antonio Iannelli*

Résumé

La prévalence des stéatopathies métaboliques est en augmentation et il s'agit d'une des trois causes majeures de cirrhose au niveau mondial. À ce jour, il n'existe pas de traitement spécifique des stéatopathies, mais la perte de poids chez les sujets obèses est un point clé dans la prise en charge. La chirurgie bariatrique a démontré des effets plutôt bénéfiques en termes de résolution de la stéatose et de la stéatohépatite. L'amélioration à long terme de la fibrose hépatique après chirurgie bariatrique est probable mais nécessite des études prospectives complémentaires. La présence d'une NASH chez un patient obèse sévère constitue une comorbidité qui justifie en elle-même la réalisation d'une chirurgie bariatrique.

INTRODUCTION

L'incidence du surpoids et de l'obésité est en constante augmentation au niveau mondial. Cette pandémie est non seulement associée au développement du diabète de type 2, de l'hypertension artérielle, des pathologies cardiovasculaires, mais aussi à une altération de la fonction hépatique. La prévalence des stéatopathies métaboliques ou *Non Alcoholic Fatty Liver Disease* (NAFLD) dans la population générale est estimée entre 5,4 et 24 % (1). La NAFLD regroupe la stéatose simple caractérisée par une surcharge de triglycérides (TG) dans le foie (présence de vacuoles lipidiques dans plus de 5 % des hépatocytes) et la stéatohépatite, caractérisée par une stéatose associée à un infiltrat inflammatoire et des lésions hépatocytaires (ballonisation et mort cellulaire) (*Non-Alcoholic Steato-Hepatitis*, NASH). La NAFLD est asymptomatique, mais ces lésions hépatiques peuvent évoluer vers une fibrose hépatique (2), voire une cirrhose (entre 10 et 30 % des sujets avec NASH développent une cirrhose dans les 10 ans), et augmentent le risque de carcinome hépatocellulaire (3). Il s'agit d'une des trois causes majeures de cirrhose (2). Le risque de décès lié au foie est également augmenté (4). Actuellement, le diagnostic de certitude est toujours histologique et nécessite donc une biopsie hépatique qui peut avoir des complications. La NAFLD représente un problème de santé publique important. La prise en charge repose essentiellement sur l'application de mesures hygiéno-diététiques car aucun médicament efficace et bien toléré au long cours n'a été validé par de grandes études prospectives. La prévalence de la NAFLD et la NASH chez les sujets obèses morbides (indice de masse corporelle [IMC] > 35 kg/m^2) est de 70 % et 30 % respectivement (5) (Fig. 1). De plus, les sujets obèses (IMC > 30 kg/m^2) sont particulièrement à risque de développer une NASH en présence d'un syndrome métabolique qui est défini par trois éléments parmi un tour de taille ≥ 94 cm chez les hommes et ≥ 80 cm chez les femmes en Europe, une hypertriglycéridémie, un taux de HDL-cholestérol abaissé, une hypertension artérielle et une hyperglycémie (6).

MÉCANISMES D'APPARITION DE LA NAFLD

Les comorbidités associées à l'obésité sont le reflet d'un état inflammatoire chronique qui est lié à l'accumulation du tissu adipeux blanc au niveau de la graisse viscérale. Le tissu adipeux blanc est considéré comme un organe endocrinien à part qui sécrète des adipocytokines et des cytokines responsables de l'état inflammatoire chez les sujets obèses.

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En effet, la prévalence de la NAFLD chez les sujets présentant un syndrome métabolique est très élevée. Chez les patients présentant une NAFLD, l'accumulation de triglycérides au niveau hépatique est entretenue par l'arrivée d'acides gras libres (AGL) provenant de la lipolyse du tissu adipeux viscéral et de la lipogenèse de novo hépatique. Ces deux phénomènes sont étroitement liés et associés à l'insulinorésistance (IR) (7).

L'IR est donc le facteur clé dans la physiopathologie du syndrome métabolique et des pathologies associées et joue donc un rôle dans le développement et la progression de la NAFLD (7). L'IR périphérique est caractérisée par une diminution de l'entrée du glucose au niveau de muscle squelettique et une diminution de la suppression de la lipolyse au niveau du tissu adipeux. Au niveau hépatique, l'IR est caractérisée par une augmentation de la néoglucogenèse et la glycogénolyse (8). L'IR est le facteur clé dans l'accumulation de graisse au niveau du foie, d'une part par l'hyperinsulinémie et d'autre part, par une augmentation de l'activité enzymatique menant à une lipogenèse de novo (Fig. 2).

Les adipokines et cytokines qui jouent un rôle important dans la NAFLD sont l'adiponectine, la leptine, le TNF-alpha et l'interleukine-6 (IL-6). L'expression de ces médiateurs est étroitement liée à l'obésité centrale. Ils jouent un rôle important dans la modulation de la voie de signalisation de l'insuline et des cascades inflammatoires. Ces deux phénomènes sont primordiaux dans l'accumulation de graisse au niveau hépatique, mais aussi dans la progression de la stéatohépatite (7).

La leptine est augmentée chez les sujets obèses et peut stimuler l'inflammation et la fibrogenèse.

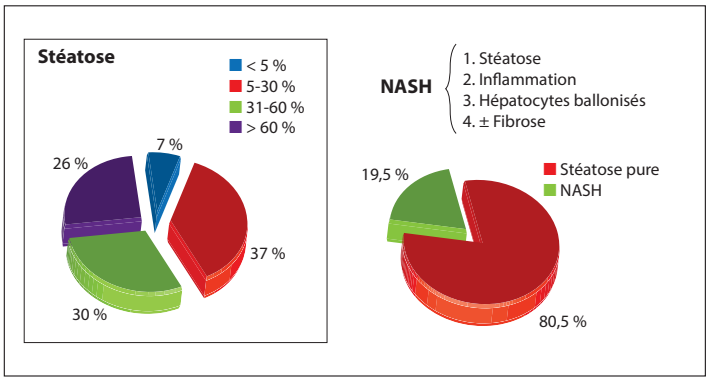

Figure 1 - NAFLD chez les sujets obèses candidats à la chirurgie bariatrique. Cohorte prospective de 815 patients obèses morbides ayant eu une chirurgie bariatrique au CHU de Nice.

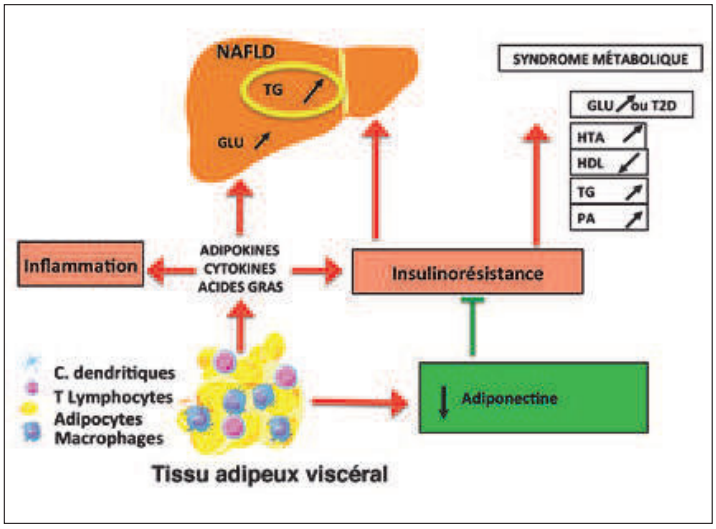

Figure 2 - Interrelations entre le foie et le tissu adipeux au cours de l'obésité. L'insulinorésistance (IR) est l'élément clé. Au niveau hépatique, l'IR est caractérisée par une augmentation de la néoglucogenèse et de la glycogénolyse. L'IR favorise l'accumulation de graisse au niveau du foie, d'une part par l'hyperinsulinémie et d'autre part par une augmentation de l'activité enzymatique menant à une lipogenèse de novo.
GLU : glucose, TG : triglycérides, HTA : hypertension artérielle, HDL : high density lipoprotein cholesterol, *PA : périmètre abdominal.*

D'autre part, l'adiponectine qui est connue pour son effet antiathérogène, anti-inflammatoire et anti-diabétogène, est diminuée lorsque l'IMC, la masse grasse et les triglycérides augmentent (9).

La bêta-oxydation mitochondriale est la voie oxydative des acides gras dans les conditions physiologiques normales. Chez les sujets atteints d'une NAFLD, ces voies sont inhibées et sont la source principale de radicaux libres (7, 9). De nombreuses études fondamentales et cliniques ont montré le lien entre la sévérité de l'atteinte hépatique

et le degré de stress oxydatif (9). Il existe une augmentation des marqueurs sériques du stress oxydatif et une diminution des molécules anti-oxydantes chez les sujets atteints d'une NASH. Le taux de ces marqueurs est corrélé à la sévérité de l'atteinte hépatique et l'IR (9).

Malgré la prévalence élevée des facteurs de risque de l'IR, il n'y a qu'un pourcentage des sujets présentant une IR qui développent une NAFLD et encore moins de sujets chez qui une NAFLD évolue vers la NASH et ses complications (10). Il semble donc exister une prédisposition génétique à développer une NAFLD qui est fortement influencée par les facteurs environnementaux.
Les mécanismes responsables de la progression d'une NAFLD vers une NASH ne sont toujours pas élucidés. Un modèle à "deux coups" a été proposé (11). La première étape dans la pathogenèse de la NAFLD est la présence d'une IR périphérique qui mène à une stéatose hépatique. L'association de l'hyperglycémie à l'hyperinsulinémie stimulerait la synthèse de novo des lipides et mènerait à des anomalies structurales au niveau des mitochondries des hépatocytes. D'autre part, l'IR du tissu adipeux augmenterait l'afflux d'AGL au niveau hépatique qui contribuerait à la stéatose. Les hépatocytes stéatosiques seraient plus vulnérables à un second "coup" qui serait induit par les cytokines (TNF-alpha) et le stress oxydatif. Ces phénomènes mèneraient à des lésions de stéatohépatite et à la fibrose (12). De plus, l'induction de CYP2E1, les endotoxines bactériennes et l'accumulation de fer au niveau hépatique pourraient jouer un rôle dans le développement de la stéatohépatite. Plus récemment, un modèle des "coups multiples", intégrant les multiples facteurs hépatiques délétères, a été proposé (13). De plus, l'aggravation des lésions n'est pas systématique et le passage entre stéatose et stéatohépatite n'est pas irréversible. Certains patients semblent garder au cours du temps une stéatose hépatique non évolutive et non associée à une surmortalité hépatique, alors que d'autres patients évolueraient rapidement vers une NASH et une fibrose hépatique altérant leur pronostic (14).

Tableau 1 - Stratégies de prise en charge au cours de la NAFLD.

Stratégie	Intervention
Perte de poids	Mesures hygiéno-diététiques Médicaments • Orlistat • Sibutramine • Rimonabant
Diminution de l'insulinorésistance	Metformine Thiazolidinediones
Antioxydants	Vitamine E Probucol
Anti-TNF	Pentoxiphylline
Autres	Acide ursodeoxycholique Antagoniste de l'angiotensine Betaine N-acétylcysteine

TRAITEMENT CLASSIQUE DE LA NAFLD

Le traitement le plus efficace d'une NAFLD ou NASH est la perte de poids. Cette perte pondérale peut être obtenue par une modification du mode de vie permettant un apport calorique moindre et une activité physique augmentée. Plusieurs agents pharmaceutiques ont été également proposés pour le traitement des NALFD, entre autres la metformine et les antioxydants. Mais aucun essai randomisé contrôlé n'a démontré un effet bénéfique avec une innocuité à long terme de ces différentes molécules sur la NAFLD (Tab. 1).

La chirurgie bariatrique est reconnue comme traitement de l'obésité morbide et a donc trouvé naturellement une place prépondérante dans la prise en charge de la NAFLD.

MÉCANISMES IMPLIQUÉS DANS LA RÉSOLUTION DE LA NAFLD APRÈS LA CHIRURGIE BARIATRIQUE

La chirurgie bariatrique est le moyen le plus efficace d'obtenir une perte pondérale à long terme. Les procédures malabsorptives telles que le court circuit gastrique (RYGB) et la diversion bilio-pancréatique avec switch duodénal (SD) permettent une perte de poids plus importante que les procédures restrictives (anneau gastrique [AG], sleeve gastrectomie [SG]), la moyenne étant une perte de poids en excès de 60 % (15).
L'AG induit une satiété en activant les mécanorécepteurs sensibles à la tension gastrique. La SG diminue la sécrétion de ghréline qui est l'hormone oréxigène sécrétée par les cellules du fundus gastrique qui est réséqué dans la SG.

Les mécanismes des procédures malabsorptives sont plus complexes et dépendent de la longueur de l'intestin court-circuité et de la modulation des peptides neuro-endocrines sécrétés. Ces derniers agissent à travers plusieurs voies de signalisation, dont la sécrétion augmentée de PYY, hormone anorexiant, suite au contact rapide des aliments avec la muqueuse de l'iléum. La sécrétion des incrétines (GLP-1, GLP-2), impliquées dans l'axe entéro-insulaire, est également augmentée. Des travaux récents ont montré que la SG s'associe aux mêmes modifications des hormones digestives que le RYGB (16). Les mécanismes impliqués dans l'amélioration ou la résolution de la NAFLD peuvent être séparés en deux groupes, ceux directement liés à la perte de poids et ceux indépendants de la restriction calorique et donc non liés à la perte pondérale (Fig. 3).

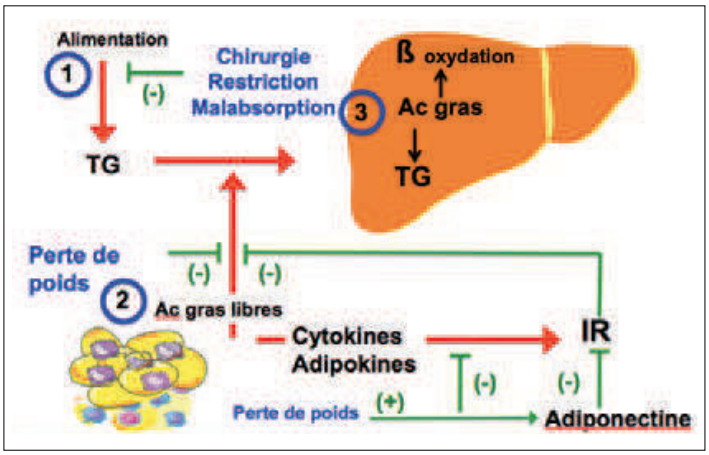

Figure 3 - Effets directs de la perte de poids sur la NAFLD. La restriction alimentaire diminue l'apport en sucres rapides. La diminution de la graisse viscérale augmente la sensitivité à l'insuline et diminue la circulation d'acides gras libres. Parallèlement, il y a une diminution des médiateurs de l'inflammation et une augmentation de l'adiponectine améliorant ainsi la sensibilité à l'insuline. Au niveau hépatique, ceci se traduit par une diminution de la néoglucogenèse, la glycogénolyse et la lipogenèse de novo.
Ac gras : acides gras, IR : insulinorésistance.

La restriction gastrique est responsable de la restriction calorique et d'une diminution des apports en sucres rapides et en graisses responsables de la dyslipidémie et de la stéatose hépatique. La perte pondérale est associée à une augmentation de la sensitivité à l'insuline qui diminue la libération d'AGL du tissu adipeux. La diminution de l'inflammation du tissu adipeux entraîne une diminution des taux plasmatiques des médiateurs de l'inflammation (adipokines et cytokines) et une augmentation du taux plasmatique d'adiponectine. Cela améliore la sensibilité à l'insuline.
Dans le modèle animal de SG, nous avons pu montrer que la SG permet une régression plus importante de la stéatose hépatique par rapport à la restriction alimentaire isolée (17). La SG et le RYGB induisent une diminution de la sécrétion postprandiale de GLP-1 qui permet une diminution de la stéatose hépatique grâce à différentes actions dont la stimulation de la sécrétion de l'insuline, la libération moindre du glucose hépatique et la diminution de la résistance à l'insuline du foie et du tissu adipeux. Le GLP-1 active également les gènes PPARα/γ qui augmentent l'oxydation hépatique des acides gras, l'exportation des lipides et la sensibilité à l'insuline. L'inflammation hépatique est diminuée en inhibant l'expression de TNFα, IL-6, IL-1β, et MCP-1 (18).
Le RYGB diminue l'IR en augmentant l'adiponectine et en modifiant la flore intestinale secondaire aux changements de la production biliaire et de l'afflux des nutriments. La nouvelle flore intestinale, avec moins de firmicutes et plus de protéobactéries, modifie le métabolisme énergétique : le métabolisme des oligosaccharides permet une production plus importante d'AG à courtes chaînes (propionate, acétate, etc.) qui stimulent l'expression des médiateurs clés de la sensibilité de l'insuline.

INDICATION DE LA CHIRURGIE BARIATRIQUE ET NASH

Selon la Haute autorité de Santé les indications de la chirurgie bariatrique sont un IMC ≥ 40 kg/m² ou bien un IMC ≥ 35 kg/m² associé à au moins une comorbidité susceptible d'être améliorée après la chirurgie (hypertension artérielle, syndrome d'apnées du sommeil, désordres métaboliques sévères, en particulier diabète de type 2, maladies ostéo-articulaires invalidantes, stéatohépatite non alcoolique) (19). La présence d'une NASH chez un patient obèse sévère constitue donc une comorbidité qui justifie en elle-même la réalisation d'une chirurgie bariatrique.

LES RÉSULTATS DE LA CHIRURGIE BARIATRIQUE SUR L'ÉTAT HÉPATIQUE

Plusieurs séries ont rapporté les résultats de la chirurgie bariatrique sur l'évolution des lésions de NAFLD voire NASH après une perte de poids massive. L'intervalle entre la biopsie hépatique initiale et la seconde biopsie varie de 10,2 à 60 mois. Les résultats sont univoques sur l'évolution de la stéatose ainsi que l'inflammation qui s'améliorent chez la majorité des patients. En revanche, l'évolution de la fibrose est moins prévisible, 3 séries ne retrouvent plus de fibrose lors de la seconde biopsie, alors que d'autres études retrouvent une aggravation du degré de fibrose. Chez les patients opérés d'une diversion bilio-pancréatique avec une perte de poids massive et rapide, l'aggravation de la fibrose peut être expliquée par une augmentation de la lipolyse qui augmente l'afflux d'AGL du tissu adipeux viscéral dans le sang portal vers le foie où ils sont métabolisés (20). Dans une série prospective, Lassailly et al. ont pu montrer une amélioration de la stéatose, l'inflammation et la fibrose chez la majorité des patients NAS ≥ 5 à 5 ans (21).

PRÉPARATION À LA CHIRURGIE BARIATRIQUE

La NAFLD complique la chirurgie bariatrique d'un point de vue technique car l'augmentation de volume du foie due à l'infiltration graisseuse rend l'accès à l'estomac et en particulier au cardia très difficile. Dans ces conditions le risque de plaie hémorragique du foie est élevé et les difficultés techniques sont responsables d'une augmentation du temps opératoire. Dans certains cas, l'accès à la partie haute de l'estomac est impossible et une partie du fundus gastrique est laissée en place en cas de SG ou de RYGB. Pour ces raisons, le patient doit être impérativement préparé avant la chirurgie. Une perte de poids préopératoire 3 à 4 semaines avant la chirurgie en raison de 5 % du poids du corps obtenu avec un régime alimentaire hypocalorique et hyperprotéiné est la stratégie généralement utilisée. Nous avons montré que la prise d'acides gras oméga-3 quatre semaines avant la chirurgie permet une diminution de 20 % du volume des segments II et III hépatiques mesurés en échographie (22).

LA CHIRURGIE BARIATRIQUE ET LA CIRRHOSE HÉPATIQUE

La possibilité de guérir la cirrhose hépatique avec la chirurgie bariatrique reste une question débattue. Les patients cirrhotiques candidats à une chirurgie bariatrique doivent être sélectionnés avec le plus grand soin. En effet, il a été montré que le risque de mortalité est multiplié par 2,2 (1-4,6) comparativement aux patients obèses non cirrhotiques lorsque la cirrhose est compensée. Ce risque est multiplié par 21,1 (5,4-82,3) lorsque la cirrhose est décompensée (23). L'existence d'un programme de transplantation hépatique et le volume de chirurgie bariatrique d'un centre sont significativement associés à une diminution du risque de mortalité du patient opéré d'une chirurgie bariatrique. Actuellement, il n'y a que quelques séries rapportant l'évolution des patients cirrhotiques opérés d'une chirurgie bariatrique. Clark et al. ont rapporté une régression significative de la fibrose chez des patients présentant une cirrhose confirmée par une biopsie et opérés d'un SD (24). En revanche, ces patients sont de potentiels candidats à une transplantation hépatique. Cela doit être pris en compte dans le choix de la procédure de chirurgie bariatrique afin de ne pas compromettre le projet de transplantation hépatique.

CONCLUSION

Chez les patients obèses morbides ou les patients obèses sévères avec une comorbidité, la chirurgie bariatrique a démontré des effets plutôt bénéfiques en termes de résolution de la stéatose et de la stéatohépatite. L'amélioration à long terme de la fibrose hépatique après chirurgie bariatrique est probable mais nécessite des études prospectives complémentaires. La présence d'une NASH chez un patient obèse sévère constitue une comorbidité qui justifie en elle-même la réalisation d'une chirurgie bariatrique. L'intérêt d'une chirurgie bariatrique "métabolique" chez des patients avec une obésité non sévère mais de multiples atteintes viscérales liées à une IR sévère (diabète compliqué, NASH...) est une voie de recherche future. ■

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Résumé

L'incidence du surpoids et de l'obésité est en constante augmentation au niveau mondial. Cette pandémie est non seulement associée au développement du diabète de type 2, de l'hypertension artérielle, des pathologies cardio-vasculaires, mais aussi à des complications hépatiques telles que la Non-Alcoholic SteatoHepatitis (NASH) qui peut évoluer vers la cirrhose et/ou le carcinome hépatocellulaire.
La sleeve gastrectomie (SG) est une opération bariatrique qui consiste à réduire le volume de l'estomac en réalisant une gastrectomie longitudinale. L'hypothèse que d'autres mécanismes indépendants de la perte de poids sont impliqués dans l'amélioration des complications hépatiques et métaboliques de l'obésité après SG a été émise. Dans un premier temps un modèle murin de SG a été mis au point et puis l'effet de la SG chez des souris C57Bl/6J soumis à un régime High Fat Diet pendant 33 semaines a été étudié chez trois groupes d'animaux : groupe *SG*, groupe *sham pair fed* (SPF, animaux alimentés avec la même quantité de nourriture consommée par les animaux du groupe SG) et groupe *sham* (animaux alimentés ad libitum). A J23 de la SG les animaux SG, SPF et Sham pesaient en moyenne 79±7,1 %, 85,15± 3 % et 99,25±4 % de leur poids initial respectivement (*p<0,001*). La prise alimentaire a été identique entre le groupe SG (1,88 g/j) et groupe SPF (1,88 g/j) et significativement inférieure au groupe sham (4,5 g/j) (*p< 0,05*). Le test de tolérance au glucose montrait une amélioration de l'insulinorésistance des animaux SG à J23. L'aire sous la courbe du groupe SG, SPF et Sham à J20 était de 5925, 11903,1 et 13140 g*min/ml respectivement (*p< 0,001*). Au niveau hépatique les animaux SG montraient une diminution significative de la stéatose (SG vs. SPF, *p< 0,05*; SPF vs. Sham, *p<0.01*). Il existe donc des mécanismes améliorant les complications hépatiques et métaboliques de l'obésité qui sont en partie indépendants de la réduction de l'apport calorique.

Dans le second volet nous avons étudié l'évolution à long terme des lésions hépatiques liées à la NASH chez des patients obèses morbides avec une NASH prouvée histologiquement (NAS score ≥ 5) lors de la chirurgie bariatrique (gastric bypass sur anse en Y (LRYGB). Dix patients (9 femmes/ 1 homme) de la cohorte prospective du Service de Chirurgie Digestive du CHU de Nice avec un âge moyen de 46,4 ± 4 ans ont été inclus dans cette étude. La deuxième biopsie a été réalisée à une médiane de 57 mois [Q1 ; Q3 : 44; 79] après le LRYGB. La perte de poids moyenne était de –13,3[–15.9; –9.3] points de l' IMC lors du suivi et tous les patients avaient perdu > 50% de leur poids en excès. La rémission du syndrome métabolique et du diabète a été observée chez 71,6 % et 100 % des patients respectivement. Le NAS score a été amélioré chez tous les patients (amélioration de la stéatose chez 100 %, de l'inflammation chez 90,9 %, de la souffrance hépatocytaire chez 90,9 % et de la fibrose chez 72,7 % des patients). Le taux sérique moyen du fragment clivé de la cytokératine 18 (M30), marqueur de l'apoptose hépatocytaire, était à 442,98 ± 92,17 U/l avant le LRYGB en faveur d'une souffrance hépatocytaire. Au moment du suivi le taux sérique du M30 était significativement baissé à 226,81 ± 8,6 U/L (*p<0,018*). Le LRYGB a permis une amélioration à long terme des lésions hépatocytaires liées à la NASH chez les patients obèses morbides. L'amélioration post-opératoire de la souffrance hépatocytaire corrèle avec la baisse du taux sérique du M30.